

AYURVEDIC HERBS

**A Clinical Guide
to the Healing Plants
of Traditional
Indian Medicine**

M. S. Premila, PhD

Ayurvedic Herbs
A Clinical Guide
to the Healing Plants
of Traditional Indian Medicine

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For my mother,
Lakshmi Sivaraman

And in memory of my father,
M. S. Sivaraman

ABOUT THE AUTHOR

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CONTENTS

Foreword	xi
<i>H. Wagner</i>	
Preface	xiii
Acknowledgments	xvii
Chapter 1. Drug Development and Evaluation in Ancient India	1
Origins of Ayurveda	1
History of Drug Evaluation	3
Plant Use in Ayurveda	4
Chapter 2. Scientific Investigation of Indian Medicinal Plants	7
History of Research	7
Results of Scientific Investigation	9
Chapter 3. Gastrointestinal Agents	13
Malabsorption Syndrome	13
Dyspepsia	16
Antiulcer Plants	20
Other Antiulcer Plants	29
Inflammatory Bowel Disease	33
Antiemetic Agents	39
Laxatives	43
Other Laxative Plants	53
Diarrhea	54
Chapter 4. Hepatoprotective Agents	61
Plant Use in Ayurveda	61
Scientific Studies	62
Viral Hepatitis	76
Other Antiviral Plants	80
Ascites	81
Chronic Cholecystitis	82

Chapter 5. Respiratory Tract Drugs	85
Plants for Bronchial Asthma	86
Upper-Respiratory Tract Infections	111
Other Plants	115
Tropical Pulmonary Eosinophilia	116
Chapter 6. Cardiovascular Drugs	119
Cardioprotective Plants	120
Hypolipidemic Plants	131
Other Hypolipidemic Plants	143
Antihypertensive Plants	144
Venous Disorders	146
Chapter 7. Urinary Tract Drugs	151
Diuretics	151
Plants for Urinary Tract Disorders	157
Chapter 8. Antirheumatic Agents	163
Rheumatoid Arthritis	163
Chapter 9. Skin and Trauma Care Agents	193
Skin Diseases	194
Leukoderma/Follicular Eczema	204
Psoriasis	207
Wound Healing Plants	211
Other Wound Healing Plants	218
Fracture Healing Plants	219
Chapter 10. Gynecological Agents	223
Galactagogue	223
Antileukorrheal Plants	225
Antimenorrhagial Plants	226
Chapter 11. Antidiabetic Agents	229
Main Plants	231
Other Plants	272
Diabetic Complications	275

Chapter 12. Central Nervous System Agents	279
Memory and Learning Enhancers	280
Parkinson's Disease	298
Sedative Plants	301
Chapter 13. <i>Rasayana</i> Drugs: Antiaging Agents, Adaptogens, and Immunostimulants	305
Tonic/Antiaging Effects	306
Other Tonic/Antiaging Plants	312
Immunostimulant Effects Against Infection	313
Other Immunostimulant Plants	316
Cancer Therapy	317
Other Plants Used in Cancer Therapy	326
Chapter 14. Dental and Ophthalmological Agents	329
Dental Health	329
Other Dental Conditions	332
Ophthalmological Agents	335
Appendix: List of Single Plants, Indications, and Chapters	343
Index	347

Foreword

In the traditional medical system of India, the herbal drugs of Ayurvedic medicine form an important mainstay in therapy. Books of Ayurvedic medicine that date even from ancient times describe primarily historical aspects, the principles of Ayurveda, and the most common plants used for the prevention and therapy of diseases. The present text by Dr. M. S. Premila thus represents enormous progress, as it offers the first critical validation of traditional Ayurvedic medicine, which includes both clinically proven formulas and medicines that urgently require further research efforts. Each of the 12 chapters, dealing with the most prominent herbal drugs, enumerates the active chemical constituents, the relevant pharmacological and clinical data, and safety information, all extensively referenced. This first approach aims at what in Western terms is called evidence-based medicine. The documentation is a valuable guide for physicians and even Western-trained clinicians who are attentive to alternative and adjunctive therapies. It is a pleasure for me to recommend this book, without reservation, to all scientists in the field of phytomedicine. I wish the book much success and broad distribution beyond India.

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Preface

Worldwide interest in Ayurveda is rapidly growing, especially in the United States, Europe, and Japan. Ayurveda, the major traditional system in India, is not just about herbs but is an entire system or a way of living aimed at achieving a state of total mental, physical, and spiritual well-being through lifestyle, diet, and drugs derived from herbs. Having worked on developing standardized and validated herbal products based on Ayurveda for around two decades, it never fails to amaze me how often Ayurvedic concepts and precepts receive scientific support. Therefore, when Professor Varro Tyler suggested a book on clinical data on Ayurvedic herbs, I was very happy to accede to his request. His suggestion was to put together the scattered information available on Western-style clinical trials on Ayurvedic herbs with descriptions, comments, and references, since there was a need for such a book owing to lack of information and limited access to these aspects.

This book attempts to bridge the knowledge gap and gather the scattered information on Ayurvedic herbs to see what scientific support there is for the traditional use of these plants. In doing so, I am aware of the fact that Ayurveda considers disease as an imbalance in *doshas*, or humors, and that healing is brought about by bringing back harmony to the “deranged” *doshas*. However, Ayurvedic herbs have also been classified according to their pharmacological action or indication. For many Ayurvedic disease entities and their symptoms described in Ayurveda, there are modern equivalent medicines; thus, there are a number of Western-style clinical studies conducted on single Ayurvedic herbs.

It has also long been my desire to be able to pull all the relevant information into a cohesive whole. The herbs have been dealt with according to body systems and indications in order to provide an easier overview.

Thus, after the two introductory chapters, which highlight the relevance of the background of Ayurveda, the herbs are covered in 12 chapters. Each chapter on herbs gives a short introduction of the Ayurvedic viewpoint, where relevant, after which the important plant monographs follow. Each plant monograph covers synonyms: names in Sanskrit, English, Hindi, and Tamil. The names are followed by a short introduction, a description of the plant and its distribution in India, traditional use, the part used as a drug, chemical constituents, pharmacology, clinical studies, and safety information.

Some herbs have names only in a particular language depending on the region where they grow predominantly. *Salacia* species, for example, have local names in Malayalam, the language used in Kerala, which are descriptive of the different species. Thus, *Salacia macroserma*, with its sprawling habit, is called *anakoranti* (*ana*: “elephant”). *Salacia oblonga* and *S. reticulata* are called *ponkoranti* (*pon*: “gold”) in reference to the yellow color of the root bark. *Salacia prinoidea* is called *cherukoranti* (*cheru*: “small”). In cases where a plant occurrence is more regional, preference is given to the local name.

At this point, it should be mentioned that large variation exists in the way local names are spelled in English, and the spelling given by an author is often retained. This happens less often with botanical names.

The description of traditional use covers the major uses; similarly, the description of the plant covers details of what is important for its use.

The chemical constituents refer to active principles, where known, or to chemical classes or compounds that on the basis of current knowledge can be considered to contribute to the activity.

Some of the plants have more than one use. Thus, the same plant may occur in more than one chapter and in more than one section of a chapter. For example, ginger (*Zingiber officinale*) is used as an anti-emetic and to treat malabsorption and finds place in two sections in Chapter 3, “Gastrointestinal agents.” Ginger also finds place in Chapter 8, “Antirheumatic agents,” for its anti-inflammatory effect. Turmeric (*Curcuma longa*) is a common ingredient of curry and is used for digestion (Chapter 3). In addition, it is used in the treatment

of arthritis (Chapter 8), for asthma (Chapter 5, “Respiratory tract drugs”) and oral cancer (Chapter 13, “*Rasayana* drugs”).

Each portion on pharmacology deals only with studies that are relevant to the indication covered. Other known pharmacological studies for different uses not relevant to the particular indication are not cited. Only uses supported by clinical studies have been included. Thus, turmeric or curcumin is mentioned in discussions of the gastrointestinal tract, anti-rheumatic agents, asthma drugs, and anticancer drugs because some supporting clinical data are available. Similarly, *Commiphora mukul*, or *guggul*, finds a place in the discussions of hypolipidemic agents and antirheumatic agents, but not under agents used for thyroid stimulation even though experimental evidence is available.

In reporting clinical trials, the Ayurvedic indication and the modern medicine correlate as given by the authors have been included. For example, the condition known as *amlapitta* in Ayurveda is characterized by such symptoms as nausea, tiredness, sour vomiting, burning in the throat, thirst, vertigo, and hyperchlorhydria. *Amlapitta* has been variously described as acid dyspepsia, nonulcer dyspepsia, and gastritis syndrome. Some of the trials reported have certain basic data missing, such as the botanical name of the drug or the doses administered. As these trials correspond to traditional uses with supporting pharmacology, they could serve as indicators for further trials and have therefore been included. In some cases, specifications for the drug used should be urgently established so that it is possible to have reproducible results. This is especially true in the case of plants that have different eco- and chemotypes, for example, *Acorus calamus* and *Phyllanthus amarus*.

In addition, there have been problems in trying to group plants for a particular indication, as some of the trials are of an exploratory nature and cover several indications such as bronchial asthma, allergic rhinitis, or viral encephalitis. These have been grouped together under the same heading because, during the trial, the plant preparation would have been tried simultaneously for other indications as well, and presently, it would fragment information if grouped separately, since available information is scarce. Therefore, plants for peptic ulcer, nonulcer dyspepsia, and gastritis are grouped under antiulcer plants.

Safety information has been summarized under each monograph. Most of the plants have not been investigated adequately by modern standards of safety. Nonetheless, the herbs have been in use for a very long time and any toxicity should have become evident by now. In addition, Ayurveda prescribes the manner in which herbs are to be used or processed before use. For example, if *Commiphora mukul* resin is not processed using *triphala*, or an equivalent method, side effects are seen. In addition, the age of the resin influences its efficacy, as mentioned in the *Sushruta Samhita*.

In order to help locate the different plants and their indications for which information is available, an appendix has been added at the back of the book. This lists the names of plants, their indications, and chapter number. The chapter number in bold face is indicative of where introductory details of the plant are given.

Also included are color plates of watercolor paintings of 12 major Ayurvedic herbs, done by me.

I hope that this book will be of use not only to health care professionals but also to anyone interested in knowing more about Ayurvedic herbs.

M. S. Premila
Chennai
3.1.2005

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First and foremost, I wish to thank my family and friends, who believed in me and gave constant encouragement, especially my mother, Mrs. Lakshmi Sivaraman.

I am grateful to Professor Varro Tyler for recommending this topic when I wrote to him with my own book suggestion. Unfortunately, he is not here to see the result. I am happy that I was able to meet him briefly in Chennai, during his very busy conference schedule in June 2001. Few of us at that time could have imagined that would be the last time we would see him.

Databases form the core of providing the numerous references that go into a book. Apart from numerous journals and my own personal literature collection, I have made extensive use of the *Medicinal and Aromatic Plants Abstracts (MAPA)* published by the National Institute of Science Communication and Information Resources NISCAIR (earlier known as Publications and Information Directorate), CSIR, New Delhi, and their earlier CD. Also very useful have been the Medline database provided by BioMedical Net (bmn) and PubMed of the National Medical Library, U.S.A. For access to some missing volumes of MAPA, I am grateful to Dr. P. K. Sehgal, CLRI, Chennai. Thanks are due also to Professor M. A. Iyengar for sending me a copy of his *Bibliography of Investigated Medicinal Plants (1950-1975)*. To obtain copies of original articles I received help from The Marketing Services Division of NISCAIR, which provides a unique service in hunting down the article and the source library and then providing photocopies. Help was also given by the National Medical Library, New Delhi, the Web site www.freemedicaljournals.com, Dr. Anju Chadha, Dr. Susan Raghavan, and Dr. M. Radhika.

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Chapter 1

Drug Development and Evaluation in Ancient India

ORIGINS OF AYURVEDA

From time immemorial, plants have been used as medicines around the world and plant-based medicines have been the mainstay of traditional societies in dealing with health problems. The global search for alternative strategies for health care has been driven by a growing dissatisfaction with the inadequacy of modern medicines in certain disease areas, notably in chronic conditions such as arthritis and asthma, and with their distressing iatrogenic effects. This dissatisfaction is combined with the urge to adopt a more natural way of relating to the world and to return to nature. The search has led to worldwide interest in the scientific validation of the therapeutic efficacy of traditional plant-based medicines.

In India there arose some 3,000 years ago one of the most comprehensive and complete systems of medicine—Ayurveda, which in its holistic approach goes beyond the mere prescription of drugs. The aim of Ayurveda is twofold: to lead a healthy life full of vigor and, in the event of disease, to bring about healing. Disease is considered to be the absence of harmony, and Ayurveda involves taking measures to restore harmony and thereby health. This is achieved through a threefold plan of lifestyle, diet, and drugs in accordance with an individual's constitution and the season. Health is not merely the absence of disease but a state of total physical, mental, spiritual, and social well-being. In Ayurveda, drugs are one component of the therapeutic

modality, and drugs of plant, mineral, and animal origin are used. However, herbs constitute approximately 70 percent of the Ayurvedic materia medica.

Ayurveda translates to “science or knowledge of life,” with *Ayur* meaning “life” and *Veda* meaning “knowledge” or “science.” Ayurveda is considered to be an auxiliary Veda (*upveda*) or sometimes as a fifth Veda, the first four being the *Rig Veda*, the *Yajur Veda*, the *Sama Veda*, and the *Atharva Veda*. The Vedas are a body of knowledge considered to be of nonhuman (divine) origin. Dismayed by the growing incidence of disease, the sages and other wise men in early times beseeched the divine creator for help in alleviating human suffering. In the tradition of the *Caraka Samhita*, the divine creator through various intermediaries transmitted the science of Ayurveda to Indra and from Indra to sages such as Bharadwaja, Atri, and others, who then taught Ayurveda to their disciples; however, in the tradition of the *Sushruta Samhita*, it is Dhanvantri who received the science from Indra.¹ A description of the first conclave on preventive health and therapeutic measures to treat disease appears in the first recorded text of Ayurveda, known as the *Caraka Samhita*, which is often dated to 700 BC. The next major texts were the *Sushruta Samhita*, which deals with surgery, and the *Astanga Hridayam* of Vagbhata. The three physicians Caraka, Sushruta, and Vagbhata together form the so-called Greater Triad, or *Brihatrayi*.

Ayurvedic drugs were chosen by a combination of observation, experiment, intuition, and discussion among scholars. The intuitive element helped to select the most suitable plants, which were tried out on domestic animals such as cats, dogs, and cows. Their use was further refined by discussion among scholars, and disputes among scholars were resolved through regular meetings. The *Caraka Samhita* speaks of such meetings in the foothills of the Himalayas. Controversy was also resolved in each case by experimentation on human beings.²

What emerged from this long period of trial and experimentation on human beings is a large number of herbs of proven clinical utility. It is the results of this experimentation that are available today in the extremely terse written form known as *sutras*.

HISTORY OF DRUG EVALUATION

Medicinal plants and herbs are an important part of the Ayurvedic formulary. The use of more than 1,700 herbs has been described in Ayurveda. It is interesting at this point to review briefly the history of plant usage—drug collection, selection, and evaluation. Great attention was paid in ancient times to ensuring the quality, safety, and efficacy of the herbs used. The chemical contents of plants vary according to soil, location, season, time of day, time of year, manner of harvesting, and further processing. It is remarkable how these aspects were delineated several hundred years ago. In the *Kasyapa Samhita*, the steps to be followed before a plant can be used as medicine are enumerated: plants must be cultivated on suitable soil, in the proper season; they must be collected at the appropriate time, ensuring the absence of damage from heat, water, insects, stools, urine, and time; and they must be collected or grown in areas away from roadsides, cemeteries, and so on.³

In terms of the proper growing season, the *Caraka Samhita* mentions that leaves are to be collected in spring (March-April) and the rainy season (July-September).⁴ Some scientific evidence corroborates this. *Adhatoda vasica* leaves are used for the treatment of coughs, colds, asthma, and bronchitis. In one study, the content of the major alkaloid and active principle and bronchodilator vasicine was analyzed throughout the year and plotted to yield a curve showing two major peaks in March-April and July-September corresponding to periods when the vasicine content was highest thereby showing good correlation with the guidelines of Caraka.⁵

The efficacy of herbs and their action was often a discussion point among scholars, with differing opinions resolved through observations on human beings. Unfortunately, the actual experimental procedures followed are no longer available to us. What have been written down are the final results of discussion and experimentation, consisting of the names of the plants to be used in various conditions and the treatment to be followed.

The tremendous regard for the safety of the drugs used and the manner in which they were to be processed led to any doubts being resolved by testing on domestic animals.⁶ Processing was considered

essential to reduce or remove toxicity and also to increase bioavailability. Many plants that are toxic or poisonous find use in Ayurveda after “purification,” or *shodana*. The tubers of *Aconitum*, for example, are often used in Ayurveda although they contain the toxic alkaloid aconitine. This is possible because the drug is processed or detoxified before it is used. Boiling *Aconitum* tubers in water converts the toxic aconitine to aconine, which is less toxic.⁷ *Commiphora mukul* gum resin is widely used in Ayurveda for the treatment of arthritis and is traditionally processed before use by boiling the resin in water or a decoction of *triphalā*, or “three fruits” (a mixture of *Terminalia chebula*, *T. belerica*, and *Emblica officinalis*). During the development of *Commiphora mukul* as a hypolipidemic agent, it was found that the crude material produced minor side effects such as skin rashes, diarrhea, and irregular menstruation. After the material was purified in the traditional manner by boiling and skimming, it no longer caused skin rashes.⁸

PLANT USE IN AYURVEDA

A large number of plants are used in Ayurveda to maintain balance and harmony so that it is possible to enjoy good health. Plants were often combined to create synergy, reduce toxicity, and increase bioavailability. Multiplant preparations were and still are generally preferred, although a large number of single drugs were also used. However, very few studies have been carried out to provide scientific support to validate these combinations, not least because of the problems associated with devising a suitable methodology to do this.

Bioavailability

It has been possible to show an increase in bioavailability when either the traditional three-spice or pungent mixture known as *trikatu* (*tri*: “three”; *katu*: “pungent”), consisting of *Piper longum* (long pepper), *P. nigrum* (pepper), and *Zingiber officinale* (ginger), is added to formulations or the major alkaloid piperine of *P. longum* and *P. nigrum* is added.^{9,10} This concept has also been used to reduce the required dosage of anti-TB drugs such as rifampicin or other drugs such as

ciprofloxacin.¹¹ Controlled studies have also shown that in healthy volunteers the absorption of nutraceuticals such as β -carotene and curcumin can be increased severalfold—by 60 percent in the case of β -carotene through the addition of small quantities of piperine¹² and 2000 percent by addition of 20 mg piperine to 2 g curcumin.¹³

Synergy

A few clinical studies have shown the beneficial effects of combining drugs. Thus, combined therapy with *Semecarpus anacardium* (*bhallatak*), *Dalbergia lanceolaria* (*gourakh*), and *Commiphora mukul* (*guggul*) showed better results in osteoarthritis, frozen shoulder, and sciatica than the individual drugs alone.¹⁴ Other examples include the addition of *Bacopa monnieri* to the combination of *Inula racemosa* and *Commiphora mukul* for the treatment of heart disease (see Chapter 6, “Cardiovascular drugs”), the combination of *Gymnema sylvestre* and *Eugenia jambolana* for diabetes (see Chapter 11, “Antidiabetic agents”), and the combination of *Zingiber officinale* and *Commiphora mukul* for arthritis (see Chapter 8, “Antirheumatic agents”).

Any scientific study of Ayurvedic herbs would benefit greatly from a study of the ideas, concepts, and pronouncements given in early Ayurvedic texts regarding plant collection, processing, combination, selection, and use to see how these correlate with present-day scientific understanding. Even a brief look at the history of Ayurveda and drug development in ancient India and at some of the concepts used in drug formulation shows much can be learned and understood from the ancient texts. Such a venture could prove to be very rewarding.

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Chapter 2

Scientific Investigation of Indian Medicinal Plants

HISTORY OF RESEARCH

The scientific investigation of Indian medicinal plants, especially of those used in Ayurveda, started in the early part of the twentieth century with the extensive investigations of Dr. R. N. Chopra. His far-reaching work and documentation in the years 1930-1950 earned him the title “Father of Indian Pharmacology.”¹⁻³ His work triggered major interest in the further exploration of the wealth of knowledge available in indigenous systems of medicine, mostly by chemical and pharmacological researchers, initially through individual effort in universities and then through team efforts in various institutions including the Indian Council of Medical Research^{4,5} and the Indian Council for Research in Indian Medicine (now the Central Council for Research in Ayurveda and Siddha).⁶ Broad-based screening of Indian medicinal plants was undertaken by the Central Drug Research Institute in Lucknow,⁷⁻⁹ and specific research into individual plants and yoga therapy was carried out at the Faculty of Indian Medicine of the Institute of Medical Sciences at the Banaras Hindu University.¹⁰ This list is not exhaustive.

The Ayurvedic literature on therapeutics and materia medica formed the basis for chemical, pharmacological, and clinical research. Important single-drug preparations and compound drugs comprising multiplant preparations were studied. The major efforts were

expended in chemical and pharmacological studies, with an emphasis on what was possible based on the available materials and research facilities. Thus, for example, chemical work generally tended to use nonpolar solvents, probably because the methodology to deal with nonpolar compounds was better developed. Later, with the awareness that aqueous decoctions and infusions were the major mode of administration, researchers realized the need to look at polar compounds such as glycosides, tannins, and sugars. Working with such compounds was made easier by advances in separation science and the development of newer adsorbents such as Sephadex and new equipment based on countercurrent chromatography. A similar trend was seen in pharmacological and clinical work. Considering that in India paucity of funds has been a major constraint, the work that has been carried out is laudable.

Far less clinical work has been performed than pharmacological and chemical studies. A review of literature published between 1950 and 1975 shows that only 1.36 percent of the entries dealt with clinical trials, compared with 17.46 percent for pharmacological studies and 63.42 percent for chemical studies.^{11,12}

Other problems include the fact that many of the clinical trials were of a preliminary or exploratory nature and were carried out on small numbers of patients. The methodology has often been far from satisfactory. In some cases, promising leads have not been followed up to confirm early results. Many of the results have been published in non-peer-reviewed journals that are difficult to access. Among the various problems faced in reporting clinical trials on herbs used in Ayurveda, one concerns relating Ayurvedic disease entities to modern parameters, or in other words the problem of Western-style clinical studies being applied to Ayurveda, which has its own concepts and basis. In addition, relatively few randomized, double-blind placebo-controlled trials have been carried out. Despite this, a tremendous amount of information has been generated that shows Ayurvedic herbs and concepts to have a very sound scientific basis. Any investigation of Ayurvedic drugs needs to look at the rationale behind their use, the mode of use, and the methods of drug collection and processing.

RESULTS OF SCIENTIFIC INVESTIGATION

As a result of scientific investigation into Ayurvedic herbs, a few trends or results can be seen.

1. There is better understanding of the specific role played by an herb.

It is now possible to understand the pharmacological profile of the drugs suited to certain disease areas so that a choice can be made with regard to the drug to be used. For example, Ayurvedic herbs for the liver are often used for the treatment of jaundice, which is a general term to describe inflammation of the liver and could result from the intake of alcohol or drugs or be of viral origin. Studies now enable better decisions to be made regarding whether a drug useful for jaundice has specific action against the Hepatitis B virus (say, by binding the Hepatitis B surface antigen), whether it is hepatoprotective or antihepatotoxic, whether it helps in liver cell regeneration, and whether it has anti-inflammatory activity or an antifibrotic effect.¹³

2. Modern methods confirm ancient concepts and use.

The gum resin of *Commiphora mukul*, or *guggul* in Sanskrit, which is widely used in arthritis, is also described as being a useful anti-obesity drug, and descriptions of its etiopathogenesis correspond remarkably well with modern ideas of how obesity arises. Research has now shown its effectiveness as a hypolipidemic agent with cholesterol-lowering properties.¹⁴

3. The elucidation of mechanisms of action explains use in different indications.

The gum resin of *Boswellia serrata* is traditionally used for a number of indications, including rheumatism, arthritis, asthma, gastrointestinal tract problems, and tumors. After the resin was shown to act to inhibit 5-lipoxygenase (and leukotriene synthesis), it was hypothesized that it would be useful in bronchial asthma, ulcerative colitis and Crohn's disease—that is, in conditions where leukotriene synthesis is considered responsible for initiation and perpetuation of the disease. This hypothesis has now been supported by clinical trials.¹⁵

4. Some crude drugs and their isolated components are COX-2 inhibitors.

COX-2 inhibitors are considered to be devoid of the usual side effects of nonsteroidal anti-inflammatory drugs (NSAIDs). Several crude drugs and their active principles have been shown to be COX-2 inhibitors, for example, turmeric, curcumin, holy basil (*Ocimum sanctum*), rosmarinic acid, and ursolic acid.¹⁶⁻¹⁸

5. Evidence supports the concept of anti-aging agents.

Two categories of drugs in Ayurveda, the *rasayana* and the *vayasthapana* drugs, are considered to be useful in reducing the effects of aging. Many of these drugs have powerful antioxidant properties.¹⁹ For example, although turmeric is not a *rasayana* drug, curcuminoids from turmeric or *Curcuma longa* have a more powerful antioxidant effect than grape seed extract.²⁰ The ancient sage Chyavan is said to have rejuvenated himself using a concoction of herbs named after him: *Chyavanprash*. The major ingredient, *Emblica officinalis* or *amla*, is a potent antioxidant. *Amla* fruit, considered to be one of the richest sources of vitamin C, also contains other potent antioxidant compounds. The role of free radical scavengers in cancer, antiaging, diabetes, and so on is well recognized today.

6. The trend is toward use of enriched fractions.

A change is taking place in the way crude drugs are used. With the introduction of many standardized herbs, enriched fractions containing larger amounts of the active components are preferred, for example, Boswellic acids from *Boswellia serrata*, curcumin from *Curcuma longa*, and picroliv from *Picrorrhiza kurroa*.

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Chapter 3

Gastrointestinal Agents

In Ayurveda, the gastrointestinal system plays a very important role in both the maintenance of health and the cause of disease, not only diseases of the gastrointestinal tract but all disorders. A weak digestion, known as *mandagni*, is considered to be the main cause of all diseases, including gastrointestinal disorders.¹ Therefore, spices and herbs have been commonly added to food or taken as drugs to improve digestion, aid absorption, and promote elimination. The two most commonly used spices in Indian cooking are ginger and turmeric. Clinical trials covering such common, classical uses are rare. However, a clinical trial has been carried out to evaluate the efficacy of ginger in malabsorption syndrome or *grahni roga*.²

MALABSORPTION SYNDROME

Zingiber officinale Roscoe
(Family: *Zingiberaceae*)

Sanskrit: Adraka (fresh), sunthi (dry)	Tamil: Inji (fresh), sukku (dry)
Hindi: Adrak (fresh), sunth (dry)	English: Ginger

Zingiber officinale, or ginger, is a slender perennial herb with rhizomes that is cultivated widely throughout India. The rhizomes are very commonly used in Ayurvedic medicine in both fresh and dry forms, though more usually in the dry form. In Sanskrit, ginger is

known as a universal medicine, or *vishwa bhesaj* (*vishwa*: universal; *bhesaj*: medicine). It is also referred to as a great medicine, or *maha aushadi* (*maha*: great; *aushadi*: medicine). The drug consists of the roots or rhizomes of the plant. Traditionally, ginger is used in Ayurveda as a stomachic, to promote digestion, and for dyspepsia, flatulence, colic, vomiting, fever, coughs, colds, asthma, gout, and chronic rheumatism. It is also used externally to treat headache and toothache and to improve blood circulation.³ The drug is approved in the *Indian Herbal Pharmacopoeia*, 2002, for its carminative, antiemetic, and anti-inflammatory properties.⁴ The use of ginger as an antiemetic is discussed later in this chapter, and its use as an anti-inflammatory agent is covered in Chapter 8 “Antirheumatic agents.”

The rhizome contains 1-2 percent of an essential oil that has a variable composition, depending upon the variety and the location of the plant, and 5-8 percent of an oleoresin. The oleoresin contains the non-volatile pungent principles, the gingerols—mainly [6]-gingerol, and also [8]-gingerol and [10]-gingerol—which vary in terms of the length of their side chain and are considered to be among the active principles. The corresponding dehydration products, the shogaols that arise from the gingerols on drying, are generally not found in the fresh plant.^{3,4}

In Ayurveda, ginger is considered to be useful at every stage of digestion: digestion (*dipan*), absorption (*pachan*), and elimination (*grahi*). Thus, it is regarded as having a role in the prevention of accumulation of toxic materials (*ama*) in the body. Ginger has been shown to increase salivary⁵ and gastric secretion,⁶ act as a cholagogue,⁷ display spasmolytic activity in animals,⁸ and increase peristalsis on oral administration.⁹ In combination with two other pungent spices, pepper and long pepper, known as *trikatu*, ginger is commonly used in Ayurveda to increase bioavailability of other drugs by promoting their absorption or by preventing their metabolism during their first passage through the liver.¹⁰

An open trial was conducted on 111 patients with *grahni roga*, or malabsorption syndrome.² Inclusion criteria were chronic history of alternating diarrhea and constipation, loss of appetite, indigestion, history of loose motions, physical weakness, and loss of weight. Three grams of dried ginger powder was given thrice daily with

warm water for 1 month. Patients were admitted as in-patients for treatment with ginger and were given a hospital diet. The duration of the disease in the patients ranged from 1 month to 7 years; 36 patients had the disease for 1 to 2 years and formed the largest group. Most patients were generally anemic and had more than four motions a day. A total of 26 patients had *Giardia* infections, and 27 patients had *Entamoeba histolytica* cysts. Treatment resulted in reduction of the number of motions to one to two per day, increase in hemoglobin levels, increase in body weight and general health, and elimination of cysts in giardiasis and amoebiasis in a majority of patients.² Thus the beneficial effect that ginger has on absorption has been revealed. However, considering the potential usefulness of the drug, further controlled studies are required.

Ginger has a low acute toxicity. In one study on mice, an alcoholic extract given at a dose of $2.5 \text{ g} \cdot \text{kg}^{-1}$ body weight (equivalent to 75 g fresh rhizome) for 7 days showed no mortality and no side effects except for mild diarrhea in two animals.¹¹ No side effects have been reported in clinical trials.¹² Experiments to test the mutagenic and antimutagenic potential of ginger and isolated constituents have shown variable results depending upon the components present and the bacterial strain used.¹³ Based on the possible mutagenic potential, some authors warn against the use of ginger during pregnancy in doses larger than the amount taken in food (1-2 g per day)^{13,14} Also, the use of ginger in conjunction with diabetic, cardiac, and anticoagulant therapy is not advocated, because synergistic effects may result from taking ginger in excessive amounts owing to the prolonged hypoglycemic activity of ginger in vivo, its positive inotropic action, and its inhibiting action on platelet aggregation).¹³ In sensitive patients, ginger may cause gastric irritation.¹³

NOTES

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DYSPEPSIA

The term *dyspepsia* is used to denote a feeling of fullness or pressing in the upper abdomen as a result of gas, leading to pain or discomfort. (See the section "Other antiulcer plants" below for *nonulcer dyspepsia*.) Reports of clinical trials use the term to denote the Ayurvedic condition known as *amlapitta*, which is associated with hyperacidity.

Curcuma longa L. (Family: Zingiberaceae)

Latin: <i>Curcuma domestica</i> Valetton	Hindi: Haldi
Sanskrit: Haridra	Tamil: Manjal
English: Turmeric	

Curcuma longa, or turmeric, is a slender perennial herb with fleshy roots. It is cultivated as an annual crop throughout the warmer parts of India. In India, turmeric is very commonly used as a spice and as an ingredient of curry, giving it a characteristic yellow color. Turmeric is also considered auspicious and is used in Hindu rituals. It is widely used by women as a cosmetic to protect the skin and prevent growth of body and facial hair.

Traditionally, it has been used as a stomachic and carminative, the powdered drug being given for flatulence and dyspepsia. It is mixed in milk and taken as an expectorant in household cough and cold remedies, and used externally either by itself or as a paste with *neem* (*Azadirachta indica*) leaves for its antiseptic and healing action. The dried rhizomes are listed in the *Indian Herbal Pharmacopoeia*, 2002, as an anti-inflammatory, stomachic, and tonic agent.¹

The rhizome contains 3-5 percent yellow coloring chemicals known as curcuminoids (curcumin, curcumin I, or diferuloylmethane [50-60 percent]); monodemethoxycurcumin, or curcumin II, and bisdemethoxycurcumin, or curcumin III, as minor constituents; 2-7 percent of an essential oil with a high content of bisabolane derivatives; and the polysaccharides ukonan A, B, and C.^{1,2}

Turmeric powder increases the mucin content of gastric juice in rabbits; it may thus exert a protective effect on the gastric mucosa in gastric disorders.³ In isolated guinea pig ileum, the soluble sodium salt of curcumin—sodium curcumin—exerts an antispasmodic effect against various spasmogens.⁴ In addition, turmeric oil suppresses the growth of some intestinal, pathogenic, and toxigenic bacteria.⁵ In vitro, curcumin at 0.05 percent concentration reduces intestinal gas formation by *Clostridium perfringens*; in vivo, curcumin at 0.1 percent concentration reduces intestinal gas formation on feeding rats along with chickpea flour—a known flatulent diet.⁶ In studies from the 1950s,⁷⁻⁹ the cholaretic and cholagogic effects of the essential oil and sodium curcumin administered intravenously were demonstrated. In more recent studies, curcuminoids and the essential oil stimulated bile secretion in isolated perfused rat liver. An increase both in the production of bile and in the bile concentration was seen.¹⁰ In a rat bile fistula model, a cholaretic effect was shown by a mixture of the three curcuminoids, by curcumin I, and also by curcumin III,

which had earlier been considered to be inactive as a choleretic.^{11,12} In cholestasis caused by cyclosporine, bisdemethoxycurcumin and the curcuminoid mixture caused a reduction in cholestasis, with the effect of bisdemethoxycurcumin being much greater than that of the mixture.¹² A potent cholagogic effect has also been reported for the essential oil.¹³

In a randomized, double-blind, study on 106 patients with acid dyspepsia, flatulent dyspepsia, or atonic dyspepsia patients were randomized to one of three groups—turmeric, placebo, or a multiplant preparation known as “Flatulence.” Thus in 38 patients 500 mg turmeric powder was given four times a day for 1 week. At the end of 7 days the group of 38 patients on turmeric showed a statistically significant difference from the placebo group (38 patients); 30 patients were on “Flatulence,” a multiplant preparation, for comparison and results comparable to turmeric were obtained.¹⁴

Another study examined 440 patients with dyspeptic symptoms of 17 weeks’ duration. Of those, 36 percent had irritable bowel syndrome, 34 percent dyspepsia, 18 percent functional disturbances of the gall bladder, and 12 percent other digestive disturbances. In addition, 78 percent of patients presented a psychosomatic disease component symptoms worsening with mental stress. The trial preparation consisted of capsules containing 81 mg of 96 percent ethanolic *Curcuma longa* extract, which extracts the active components—the essential oil and the curcuminoids. Two capsules were given daily for 4 weeks. The results showed a definite reduction (67.8 percent) in dyspeptic symptoms, especially pain in the upper and lower abdomen, the feeling of pressure, the feeling of fullness, and abdominal bloating. Most patients could feel a difference after an average of 6 days of treatment. The good compliance was attributed to the dosage schedule of only two capsules per day. In addition, the global tolerance was evaluated by 95.3 percent of patients as either “excellent” or “very good.”^{15,16}

Turmeric is generally regarded as safe. In individuals not previously exposed to turmeric the possibility of allergic reactions has been reported,¹ although turmeric is itself considered to have an anti-allergic effect. The literature on the safety of turmeric and curcumin has been extensively reviewed, and they have been found to be safe even at high doses. However, turmeric can cause gastric irritation in

susceptible individuals.¹⁷ In a trial on patients with bronchial asthma who were given 12 g·day⁻¹ of turmeric powder, a few patients complained of dryness of the mouth and throat, which was assuaged by a reduction of the dose.¹⁸

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ANTIULCER PLANTS

Peptic ulcers are a chronic disorder of the gut caused by a number of predisposing factors such as stress, genetic factors, acid pepsin secretion, and mucosal resistance. The bacterium *Helicobacter pylori* and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) are considered major contributory factors.¹ Peptic ulcer has been equated with the disease entity known as *parinam shula* in Ayurveda. Hyperacidity, or *amlapitta*, is considered to form part of the same spectrum and is therefore often included as part of the same clinical trials. A number of plants have been used in Ayurveda for the management of the two conditions.²

***Asparagus racemosus* Willd. (Family: Liliaceae)**

Sanskrit: Shatavari	Tamil: Ammaikodi
Hindi: Satavari	English: Asparagus

Asparagus racemosus, or *shatavari*, is a much-branched, extensive, spinous climbing shrub that is covered with a mass of small white flowers after the rains. It has numerous succulent tuberous roots that form the drug. It is found throughout the tropical and subtropical parts of India. *Shatavari* is best known for promoting milk production and for helping a pregnancy run to its full term. Its use in protecting the stomach against irritation is also well known. Despite the widespread use of *shatavari* as a nutritive tonic, only limited scientific information is available. It is mentioned in the ancient texts as being useful for peptic ulcers. A number of saponins have been

isolated from the roots and of these shatavarin IV has been shown to have antioxytotic activity.³

Asparagus racemosus has been shown to exert a protective effect in experimentally induced abdominal sepsis in rats.⁴

Many minor studies have been conducted with few patients by different authors and it is deduced that there seems to be a beneficial effect of *shatavari* on ulcers. However, more major studies are needed with greater numbers of patients and dose-searching studies to better delineate both the quality of the drug and the dosage required.

In an exploratory study, *shatavari* was given in doses of four 0.5 g tablets of root powder six times a day in a number of conditions diagnosed by Ayurvedic and allopathic doctors to be *amlapitta* (hyperacidity), *parinam shool* (peptic ulcer), *pitaj shool* (acute or chronic gastritis) *vataj shool* (spastic colon), *kaphaj shool* (flatulence), *atisar* (diarrhea), *pravahika* (dysentery), *grahani* (amebic or ulcerative colitis), and was found to be more effective in acute diarrhea, dysentery and gastritis, and in some cases of gastric ulcer and hyperacidity.⁵ Three grams of *shatavari* root powder was given four times a day to 32 patients with proven duodenal ulcer for an average of 6 weeks. Most of the patients were relieved of the distressing symptoms. It did not exhibit any antacid activity. This effect was attributed to *shatavari*'s direct healing effect on ulcers by strengthening the mucosal resistance or by cytoprotection.⁶ It has also been shown to help heal duodenal ulcers. Twenty-three patients with duodenal ulcer were treated with 25 mL of freshly expressed juice of *Asparagus racemosus* roots with 10 mL of honey 2-3 times a day for 45 days along with specific diet. Fourteen patients had complete relief, seven patients felt partial relief, and there were two dropouts.⁷ Twenty patients with duodenal ulcer confirmed by Barium meal, X-ray, and gastric analysis were given 20 g per day of *shatavari* root powder in three divided doses with milk for 1 month. Of the 20 patients, 15 had hyperacidity, whereas the remaining 5 had normal levels of gastric acidity. There was significant reduction in total acids and free hydrochloric acid of gastric juice. The results were evaluated as "excellent" in 50 percent and "good" in 30 percent of duodenal ulcer cases although 15 percent showed poor response.⁸ In eight healthy normal male volunteers, 2 g of *shatavari* was found to be equally effective in

accelerating the gastric emptying as metoclopramide, a drug used in dyspepsia.⁹

A clinical trial was conducted on 109 patients with acid dyspepsia (*amlapitta*) in order to compare the efficacy of three different *shatavari* preparations—the single drug, *shatavari* in combination with other herbs, and a herbomineral preparation. All the three preparations were found equally effective; efficacy not being altered by addition of either herbs or minerals.¹⁰

In doses used clinically, no adverse reactions have been reported.¹¹ Using two species and dose levels of 50 mg·kg⁻¹ to 1 g·kg⁻¹ body weight, the acute (for 72 hours) and subacute toxicity (for 4 weeks) of the aqueous extract has been studied and found to be nontoxic. No organ toxicity was seen and there was improvement in phagocytic and killing capacity of monocytes and polymorphonuclear cells.¹²

***Emblica officinalis* Gaertn. (Family: *Euphorbiaceae*)**

Latin: <i>Phyllanthus emblica</i> Linn.	Tamil: Nelli
Sanskrit: Amalaki	Hindi: Amla
English: Indian gooseberry, Emblc myrobalan	

Emblica officinalis (see Plate 1 in color gallery) is a medium-sized deciduous tree found both in the wild and cultivated throughout the tropical parts of India up to an elevation of 1,500 m. The yellowish green fruits are borne in bunches and are used widely in Indian cuisine to make preserves—jams, pickles, or wedges—sun-dried in order to ensure a supply throughout the year when the tree is not in fruit. The fruits of *amalaki* occupy a prominent place in Ayurveda, well known for its powerful antioxidant effect and for its high content of Vitamin C, several fold that of orange. The drug consists of the fresh and dried fruits. The fruits are listed in the *Indian Herbal Pharmacopoeia*, 2002, as antacid.¹³

The fruit contains Vitamin C, pectin, a number of polyphenolic compounds, gallic acid, ellagic acid, corilagin, alkaloids—phyllantidine and phyllantine.¹⁴ Hydrolysable tannins punigluconin,

pedunculagin, emblicanin A and B have been isolated from fresh pericarp of the fruit.¹⁵ It has been suggested that there is no Vitamin C present in the fruit based on experiments.¹⁵

The ethyl acetate-soluble fraction of the methanolic extract of *amalaki* at 50 mg·kg⁻¹ body weight when tested on albino rats showed anti-ulcer and antisecretory activity. In addition, three compounds active at 10 mg·kg⁻¹ body weight were isolated that prevented stress ulcers in albino rats. The ethyl acetate and the three compounds showed H⁺K⁺ATPase activity.¹⁶ Extracts of *amalaki* have been shown to have a healing effect on peptic ulcer in rats and humans. In a study published as abstract, patients with peptic ulcer who received 3 g of the drug twice a day after food for 15 days showed endoscopic improvement.¹⁷

In a pilot study, 20 patients with gastritis syndrome (*amlapitta*), which is characterized by pain in the epigastric region, nausea, acid eructation, and burning sensation in the abdomen, were chosen for the study. Before the study, patients were kept as in-patients on a restricted diet for 5 days and gastric analysis was done on the sixth day, after which therapy was started. Patients were kept on a restricted bland diet of milk and *chapattis*—a kind of unleavened bread. Powdered *amalaki* was given to patients at dose of 3 g thrice a day for 7 days. On the eighth day gastric analysis was done to find out changes in the gastric acidity. Most patients showed relief in symptoms from the second day with relief in all patients within 2-5 days of taking the drug. The level of acidity also came back to normal levels in most of the cases. However, the drug was effective only in cases of hyperchlorhydria and not in cases with hypochlorhydria.¹⁸

An open comparative trial examined 38 patients with dyspepsia: 10 with ulcer and 28 without ulcer.¹⁹ Patients were included in the trial if they had at least four of the following nine symptoms for a minimum of 2 weeks during the last 8 weeks prior to the entry into the study—belching, abdominal distension, feeling of fullness after meals, upper gastric burning, heartburn, regurgitation of bitter fluid, nausea, vomiting, and inability to finish normal meals. Parasitic infections were excluded by testing. In the ulcer dyspepsia group of 10 cases, patients were assigned to one of two treatment groups—five patients were given 3 g of *amalaki* powder three times a day for

4 weeks and five patients were given 30 ml gel antacid every 3 hour daily for 4 weeks. Endoscopically all five patients in the antacid group showed healing, whereas in the *amalaki* group four out of five patients showed evidence of complete healing.

In the nonulcer dyspepsia group with peak acid output between 16 and 40 mEq·h⁻¹ patients were again divided into two groups: 15 on antacids and 13 on *amalaki*. *Amalaki* produced a significant improvement in dyspeptic symptoms and a decrease in acid output, both treatment modalities being comparable. Four patients on antacids complained of pain and weakness of lower limbs, whereas three patients on *amalaki* had vomiting and loose motions controlled in 2 days without stopping the drug. *Amalaki* is a known mild laxative. It has earlier been suggested²⁰ that *amalaki* strengthens the gastric and duodenal mucosa leading to rapid healing of the ulcers. Considering the high tannin content of *amalaki* this is likely to be the case, with the tannin forming a protective covering allowing the ulcer to heal underneath.

In another preliminary trial²⁰ 39 cases of duodenal ulcer and 21 cases of nonulcer dyspepsia were given 3 g of *amalaki rasayana* with water thrice daily for 10 days initially and subsequently twice daily. No other drug—antacid, tranquillizer, or anticholinergic drug was given during this period. *Amalaki rasayana* is a traditional Ayurvedic preparation obtained by adding a decoction of *amalaki* to the fruit powder and drying it. This process of adding the decoction and drying is repeated 21 times. Patients were selected after Barium meal, X-ray, and the history of their disease. Normal diet was advised with restrictions on sour, fried, and very spicy food, large quantities of rice and pulses. In cases of intolerable pain, a bland diet of milk and unleavened bread (*chapattis*) was advised. The duration of the complaint ranged from 6 weeks to 12 years. It was found that there was marked relief from pain within 2-10 days of treatment in 82 percent of the cases. There was also relief in other symptoms like pyrosis, flatulence, reduced appetite, constipation, vomiting, heme-temesis, and melena in a majority of cases.

Amalaki fruits are considered safe and have been used for a very long time in India, for their health benefits, in the form of food items like pickles, dried fruit powder mixed in yogurt, or just preserved in

honey. In long-term trials a few patients complained of loose motions and nausea, which was controlled without stopping the drug, attributable to the known laxative effect of the *amalaki*.¹⁹ The acute and subacute toxicity of *Embllica officinalis* has neither revealed any toxic effect nor was any toxic effect seen on liver and kidney, and it improved the phagocytic and killing capacity of monocytes and polymorphonuclear cells.²¹ No cellular toxicity was seen when added to fresh sheep erythrocytes.²² The aqueous extract showed potent antimutagenic activity in vitro.²³

Musa sapientum L. var. paradisiaca (Family: Musaceae)

Sanskrit: Kadali	Tamil: Vazhai
Hindi: Kela	English: Banana, plantain

Musa sapientum var. paradisiaca is cultivated throughout India for culinary use. The unripe fruits are commonly cooked and eaten as a vegetable in India. They are also considered to be useful for gastric disorders.²⁴

Both raw and ripe banana skin and pulp contain 5-hydroxytryptamine, with maximum content in raw fruit pulp.²⁵ The pulp is rich in flavonoids, mostly leucoanthocyanidins especially leucodelphinidin and leucocyanidin.²⁶ Leucocyanidin obtained from the pulp has been shown to exhibit a significant protective effect against aspirin-induced ulcers.²⁷

Banana's antiulcerogenic effect in different small animal models has been summarized²⁸—those using histamine in guinea pigs^{25,29} and mice,³⁰ phenylbutazone-induced gastric ulcers in guinea pigs,^{31,32} in restraint ulcers in rats,^{33,34} aspirin-induced gastric ulcer in rats^{35,36} and those using Thai *Musa* species.³⁷

Banana powder presumably acts by strengthening the mucosal resistance against ulcerogens^{28,38} and promotes healing by inducing cell proliferation²⁸ and increasing cellular mucus.³⁸ To obtain an active powder, drying of the pulp is best done below 40°C.²⁷ An active extract is obtained by extraction with water^{27,35} or aqueous alcohol³⁵ at temperatures below 50°C, beyond which activity is lost. The aqueous

extract is rich in leucocyanidin, which is an active compound.²⁷ Other components of green banana like pectin and phosphatidyl choline may protect the gastric mucosa by adding strength to the mucous phospholipid layer.³⁶ An ethanol extract increases eicosanoids accumulation in human gastric mucosa.³⁹ The anti-ulcerative activity of banana is influenced by the type of soil, season, maturity and species.⁴⁰

An open clinical trial carried out on 24 peptic ulcer patients (2 gastric and 22 duodenal ulcer) with radiologically or endoscopically confirmed diagnosis. Banana powder at a dose level of 1 g four times a day was given half an hour before meals for 12 weeks. A total of 19 patients completed the treatment. Of the patients 84 percent showed symptomatic relief.⁴¹ In a double-blind, multicentric study, there was complete healing in 70 percent patients as determined endoscopically compared to 40 percent in the placebo group. In the treatment group, 24 percent showed partial healing, whereas no partial healing was observed in the placebo group.⁴²

Green bananas are commonly eaten as a vegetable in India and are considered to be safe without any adverse effects. There appear to be no specific studies on the toxicity of the fruit although some information is available on the leaf and stem alkali.⁴³

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OTHER ANTIULCER PLANTS

The exploratory clinical evaluation of some other plants at Banaras Hindu University have been summarized.¹ Thus *Adhatoda vasica*, *Eclipta alba*, and *Glycyrrhiza glabra* have been tried out on small groups of patients.

Adhatoda vasica Nees (Family: Acanthaceae)

Latin: *Adhatoda zeylanica* Medicus,
Justicia adhatoda Linn.

Hindi: Arusa

Sanskrit: Vasa

Tamil: Adhatodai

English: Malabar Nut Tree

The leaves of *Adhatoda vasica* or *vasa* are widely used for the treatment of cough, cold, and asthma (see Chapter 5, “Respiratory tract drugs”). The plant is reputed in Ayurveda for use in bleeding disorders and hence it was tried out in cases of “*amlapitta*,” which was earlier explicated as nonulcer acid dyspepsia in modern parlance.² Thus 20 patients of hyperacidity and hyperchlorhydria were treated as in-patients and given *vasa* as a syrup—three teaspoons four times a day equivalent to 30 g per day of crude drug in four divided doses for 6 weeks. Symptoms were carefully recorded. There was clinical improvement and reduction in the free and total gastric acidity, with 85 percent responding “well” to treatment. The assessment was that 7 patients were cured and 10 improved, whereas 3 remained unchanged.³

Eclipta alba (Linn.) Hassk (Family: Asteraceae)

Latin: *Eclipta erecta* Linn, *Eclipta prostrata* Linn.

Hindi: Bhangra

Sanskrit: Bhringaraja, Kesharaja

Tamil: Karasalanganni

English: Trailing eclipta

This plant is well known in Ayurveda for its hepatoprotective activity and has been covered in Chapter 4 “Hepatoprotective agents.” *Eclipta alba* juice is used as a soaking agent in various Ayurvedic antiulcer preparations. A series of studies were conducted in Banaras Hindu University to evaluate the efficacy of the drug in nonulcer dyspepsia and duodenal ulcer.

In an exploratory study, 22 patients with nonulcer dyspepsia and 8 patients with duodenal ulcer were given *Eclipta alba* whole plant as a syrup in a dose of 20 ml·day⁻¹ (from 20 g crude drug) in two divided doses for 6 weeks. Of dyspeptic patients 90 percent were cured and improvement was seen in 87 percent of ulcer patients.⁴

As a result of these findings, 60 patients were given 30 g of the whole-plant powder in three divided doses. Thus 35 cases of nonulcer dyspepsia received the drug for a period of 1 month and 25 patients with duodenal ulcer were administered the drug for a period of 3 months. Most of the patients showed marked symptomatic relief. Patients with nonulcer dyspepsia were relieved of epigastric pain, nausea, and throat burning, whereas patients with peptic ulcer were relieved of nocturnal pain, acid reflex and nausea. Both groups showed significant reduction in gastric acidity with 80 percent of patients with nonulcer dyspepsia showing good response. Radiological improvement was observed in 75 percent of patients who were followed up. It was assessed that excellent results were obtained with 48 percent of patients with duodenal ulcer.⁵ However, considering the small number of patients, the large dosage of 30 g of drug used, and given the fact that *Eclipta alba* contains wedelolactone that is a potent 5-lipoxygenase inhibitor, further studies are needed to evaluate the usefulness of the drug.⁶ Subsequently, in another study the same dosage of 30 g of whole-plant powder was given to 35 cases with duodenal ulcer for a period of 3-6 months and found to be effective in 60 percent of the cases.⁷

***Glycyrrhiza glabra* Linn. (Family: Fabaceae)**

Sanskrit: Yashtimadhu

Tamil: Atimadhuram

Hindi: Mulethi

English: Liquorice, licorice

Rhizomes and roots of *Glycyrrhiza glabra* are commonly used in Ayurveda in cough remedies, skin preparations, and in combination with other plants for the treatment of ulcer. The drug is approved in the *Indian Herbal Pharmacopoeia*, 2002, for its anti-inflammatory activity and its antiulcer effect.⁸ The major constituents^{9,10} are the triterpenoid glycyrrhizin, which is the sweet-tasting calcium and potassium salt of glycyrrhizic acid and numerous flavonoids, of which liquiritin is the major constituent that on hydrolysis yields liquiritigenin and isoliquiritigenin.

In a study on 10 cases of nonulcer dyspepsia and 15 cases of peptic ulcer, 2 g of drug powder was given thrice daily for 1 month to the nonulcer dyspepsia group and 3 g thrice a day was given for 3 months to the peptic ulcer group. There was considerable symptomatic improvement and reduction in gastric acidity. In the nonulcer dyspepsia group, 30 percent showed excellent response and 30 percent showed good response. Most patients of peptic ulcer showed more than 50 percent radiological improvement, in addition to reduction in duodenal spasm and other symptomatic improvement.^{11,12}

Extracts of *Glycyrrhiza glabra* were tested for antiulcerogenic activity against indomethacin-induced gastric ulcers in rats and their antisecretory and cytoprotective activity. The extract showed a dose-dependent antiulcerogenic activity associated with a reduced acid output and an increased mucin secretion, an increase in prostaglandin E₂ release and a decrease in leukotriene. It has been suggested that the cytoprotective effect may be due to the flavonoids present, which act as free radical scavengers.¹³ The flavonoids glabridin and glabrene inhibited in vitro the growth of *Helicobacter pylori*.¹⁴

The use of *Glycyrrhiza glabra* can cause water retention, edema, and an increase in the blood pressure because of its corticosteroidal effect. This effect is due to deficiency or inhibition of 11- β -hydroxysteroid dehydrogenase,¹⁵ an enzyme that catalyzes conversion of cortisol to cortisone, by a metabolite of glycyrrhetic acid, 3-monoglucuronylglycyrrhetic acid,¹⁶ as a result of which cortisol levels increase in the kidney. In other parts of the world the use of deglycyrrhinated licorice (with glycyrrhizin removed) is preferred for the treatment of ulcers. Its use is not recommended for patients with high blood pressure, heart disease, and diabetes, problems with the kidney

or liver, and for periods exceeding 4-6 weeks. Recommended average daily doses of crude root range from 5 to 15 g corresponding to 200-800 mg of glycyrrhizin.¹⁷ In Ayurveda licorice is generally combined with other plants in antiulcer preparations and therefore dosage is reduced to lower and hence safer levels.

This was also noted in the trial of Revers,¹⁸ who noted that 20 percent of peptic ulcer patients treated with a paste containing 40 percent licorice suffered from edema, which disappeared on discontinuation of the drug.

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INFLAMMATORY BOWEL DISEASE

Ulcerative colitis and Crohn's disease are two chronic inflammatory bowel diseases whose incidence is increasing in the West. Seen mostly in young adults,¹ it is the cause of much morbidity. It is believed that the increased formation of the inflammatory mediators known as leukotrienes plays an important role in causing and maintaining chronic inflammation. Therefore attempts have been made to find specific inhibitors of leukotriene synthesis. However, such products, on evaluation showed unsuitable attributes like poor bio-availability, susceptibility to oxidation, side effects and were toxic.² The gum resin of the tree *Boswellia serrata*, shown to be a specific inhibitor of leukotriene synthesis, is used in Ayurveda in a variety of inflammatory conditions.³

***Boswellia serrata* Roxb. ex Coleb (Family: *Burseraceae*)**

 Latin: *Boswellia glabra* Roxb.

 Hindi: *Salai guggul*

Sanskrit: Sallaki

Tamil: Parangi sambrani

 English: Indian Frankincense,
Indian Olibanum

Boswellia serrata or *salai guggul* (see Plate 2 in color gallery) is a medium-sized, deciduous tree that grows to a height of 17 m found throughout India in the dry hilly forests. The gum resin is found under the bark and is obtained by peeling the bark or by making an incision and allowing the gum to flow out, which is collected after 1 month.⁴ The gum resin from the tree has been prescribed in Ayurveda for a variety of inflammatory conditions. It is used in rheumatism, skin diseases, asthma, diarrhea, and dysentery, etc.^{5,6}

The gum resin contains essential oil, terpenoids, and gum. The active portion of the gum resin are the boswellic acids— β -boswellic acid, acetyl- β -boswellic acid, and especially what are now considered the main active principles 11-keto- β -boswellic acid and acetyl-11-keto- β -boswellic acid.⁷

In Ayurveda, *salai guggul* is considered to be a useful anti-inflammatory and antiarthritic drug. The gum resin shows a potent analgesic and sedative effect in small animals.⁸ The alcoholic extract of *salai guggul* has a marked anti-inflammatory effect in rats and mice.⁹ The alcoholic extract, as shown later by Ammon *et al.*, inhibits formation of leukotriene B₄ (LTB₄) and other 5-lipoxygenase products in isolated rat peritoneal neutrophils.¹⁰ The boswellic acids more specifically acetyl-11-keto- β -boswellic acid (AKBA) was found to be the most active in inhibiting leukotriene synthesis.⁷ They act by binding to a pentacyclic triterpene selective effector site, thereby inhibiting 5-lipoxygenase, and in turn inhibiting the synthesis of leukotrienes, while having no action on the synthesis of prostaglandins.¹¹ Apart from the inhibition of leukotriene synthesis, there is inhibition of leukocyte elastase, which causes damage in arthritis.¹² In an experimental model of inflammatory bowel disease in rats, *Boswellia* extract or AKBA was seen to cause significant reduction

of inflammation associated with indomethacin administration.¹³ In addition, boswellic acids have been shown to inhibit the complement system, which is another inflammatory mediator.¹⁴

Boswellic acids are selective and specific inhibitors of leukotriene synthesis. Therefore, they can be useful in a number of disease conditions in which increased leukotriene formation is considered to cause and perpetuate inflammation, for example polyarthritis and bronchial asthma, and inflammatory bowel diseases like Crohn's disease, chronic colitis, and ulcerative colitis. They have also been used to treat edema associated with certain brain tumors like astrocytoma and glioma.

These conditions have been clinically evaluated and are covered in the relevant chapter. Crohn's disease, ulcerative colitis, and chronic colitis are covered in this chapter. Asthma is covered in Chapter 5, arthritis is covered in Chapter 8 "Anti-rheumatic agents," and the brain tumor edema trials are covered in Chapter 13. Other disease conditions in which enhanced leukotriene synthesis plays a role are psoriasis, urticaria, allergic rhinitis, multiple sclerosis, lupus erythromatosus, myocardial ischemia, and muscividosiis. These have not yet been clinically evaluated.

Crohn's disease

In a randomized double blind trial,¹⁵ 102 patients were treated with the *Boswellia* extract H15 or mesalazine for 8 weeks. A detailed history was recorded before start of the trial and clinical symptoms and laboratory parameters were noted. Patients also maintained a diary regarding their health, stool frequency and consistency, and occurrence of stomach pain based on which their status was evaluated using Crohn Disease Activity (CDA) index. Eighty-three patients completed the study, of which 44 patients received one 400 mg tablet containing a standardized *Boswellia serrata* extract three times a day. In the comparative group, 33 patients received thrice daily 1,500 mg mesalazine. Patients were followed up every 2 weeks by checking the diary entries and by determination of the CDA index.

The improvement in the CDA index was definitely better in the case of the *Boswellia serrata* extract, however, when computed statistically, was not significant. The side-effect profile of *Boswellia*

serrata was better than mesalazine, with four infections in the case of *Boswellia serrata* as compared to eight with mesalazine. Considering that treatment with mesalazine is considered state-of-the-art treatment for Crohn's disease and that the *Boswellia* extract is as good as mesalazine, with a better side-effect profile, treatment with *Boswellia* extract H15 must be evaluated better than mesalazine based on the favorable benefit-risk advantage that it offers.

There are certain other substances in *Salai guggul* that enhance leukotriene synthesis and worsen the clinical picture. Therefore, the intake of *Salai guggul* extracts needs to be supervised by a doctor. In addition, there is in vitro evidence that there is a concentration-dependent inhibition or potentiation of 5-lipoxygenase.¹⁶

Ulcerative colitis

Ulcerative colitis is a nonspecific chronic inflammatory disease of the bowel, which can attack the entire colon from the rectum upwards. Usually, however, it is the lateral part of the intestines that is affected. With no cure, episodes of acute phase alternate with periods of remission. The disease is characterized by blood in the stools, pain, etc. It is treated with steroids in the acute phase and 5-amino-salicylic acid derivatives in the remission phase and also during the acute phase.¹⁷

In an open study, patients with ulcerative colitis grade II and III were treated with 350 mg *Boswellia serrata* extract thrice daily or 1 g sulfasalazine thrice daily for 6 weeks. There was marked reduction in loose motions, mucous in stool, blood in stool, and abdominal pain. Improvement was also seen in the inflammatory appearance of the intestinal mucosa—in crypts, abscess, and erosion of the mucosa. A total of 30 patients were examined in the *Boswellia* group. Results in both arms of the trial were comparable, with 82 percent remission in the resin group and 75 percent in the sulfasalazine group.¹⁸

Chronic colitis

Chronic colitis is a variant of ulcerative colitis characterized by vague lower abdominal pain, rectal bleeding with diarrhea, and tender palpable colon. In an open nonrandomized clinical trial, 30 patients

with chronic colitis were included in the study. Twenty patients received 300 mg of a preparation from *Boswellia serrata* gum resin thrice daily for 6 weeks, and ten patients received 1 g of sulfasalazine thrice daily for 6 weeks and served as controls. Of the 20 patients on *Boswellia* 18 showed improvement, while in the control group six out of ten patients showed improvement. The remission rate was 14 out of 20 for *Boswellia* and it was four out of ten in the sulfasalazine group.¹⁹

The LD₅₀ of an alcoholic extract was greater than 2 g·kg⁻¹ body weight. No significant effect was seen on the cardiovascular, respiratory, and central nervous systems.¹⁰ In a chronic study with controls on monkeys using the defatted alcoholic extract of *Boswellia serrata* at three dose levels, namely at two, five, and ten times the ED₅₀ for 6 months, was found not to produce any biochemical, hematological, and histopathological toxicity.²⁰ In a small percentage of patients, gastrointestinal side effects like heart burn and hyperacidity are seen that increase with increasing dosage.²¹ Also seen is skin irritation.²¹

In the clinical study on ulcerative colitis with a dose of 350 mg thrice daily for 6 weeks 6 patients out of 34 patients complained of heart burn and loss of appetite. In the bronchial asthma trial (see Chapter 5) with 300 mg thrice daily 2 out of 40 patients complained of epigastric pain, nausea and hyperacidity. In the glioblastoma trial (see Chapter 13, section "Cancer therapy," note 18) with increased dosages up to 1,200 mg thrice daily some patients complained of nausea and vomiting and two patients complained of skin irritation, which was reversible on stoppage. In the trial with children, no side effects were seen when they received a maximum dose of 126 mg·kg⁻¹ bodyweight (see Chapter 13, section "Cancer therapy," note 20) and also in the trial of Streffer²¹ (see also Chapter 13, section "Cancer therapy," note 19).

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ANTIEMETIC AGENTS

Nausea and vomiting can arise from indigestion, motion sickness, as a side effect of medicines used in cancer chemotherapy, in pregnancy in the form of morning sickness, anticipatory nausea, infections, certain internal endocrinological and neurological disorders, and after surgery.¹ In allopathic medicine, depending on the cause of nausea, different drugs are employed. Some of the drugs used to combat nausea are antihistaminic in nature and therefore cause drowsiness and loss of alertness. However, ginger has been shown to have wide-ranging antiemetic effects, without these side effects.

Zingiber officinale Roscoe (Family: Zingiberaceae)

Sanskrit: Adraka (fresh), Sunthi (dry)	Tamil: Inji (fresh), sukku (dry)
Hindi: Adrak (fresh), sunth (dry)	English: Ginger

Ginger is widely used in Ayurveda for its antiemetic effects. Fresh ginger is cut into small bits and taken along with honey, or fresh ginger juice is combined with lime and/or lemon juice in the form of syrup and taken to treat morning sickness. There is concern in Germany that ginger could cause problems in pregnancy not only because of the reported mutagenicity of ginger in certain test systems² but also because of the possibility of testosterone binding.³ There are also reports that ginger has antimutagenic potential.²

Motion and sea sickness

The first reports of the use of ginger in motion sickness, caused by a motorized revolving chair, observed that 940 mg of powdered ginger root proved more effective than 100 mg Dramamine

(dimenhydrinate) in reducing the gastrointestinal effects of motion sickness without the drowsiness caused by Dramamine. The study concluded that ginger was acting directly on the gastrointestinal tract increasing gastrointestinal motility and absorption of neutralizing toxins and acids, and not by its central action on the vomiting center.⁴

The use of powdered ginger as a prophylactic in seasickness has been studied in a double-blind randomized study with 80 cadets. One gram of ginger powder as a single dose was statistically better than placebo in reducing the incidence of vomiting and cold sweating 4 hours after ingestion.⁵ In another trial with 1,741 volunteers, ginger powder when compared with seven other OTC and prescription antiemetic drugs proved equally effective as the tested drugs.⁶

Other studies⁷⁻¹⁰ that investigated the effect of ginger on motion sickness have been divided in their opinion as to the effectiveness of the prophylactic use of ginger root in preventing nausea and vomiting. The varying results could arise from the variable quality or, as has been suggested,¹¹ because of the different focus in the trials—thus trials, which looked at the gastrointestinal effects reported better results as compared with trials that looked at the response of the central nervous system.¹¹ Positive results have been obtained using a standardized ginger root powder in two double-blind studies^{12,13} one trial being conducted in children in the age group of four to eight years, who were susceptible to motion sickness when travelling in a bus, train, or on the merry-go-round. Doses were varied from 250 to 500 mg of ginger depending upon the age of the children and given half an hour before travel and repeated if necessary every 4 hours.¹³

Hyperemesis gravidarum

In a double-blind randomized crossover trial 250 mg powdered ginger four times a day for 4 days was compared against placebo given in a similar capsule also four times a day to 30 patients suffering from severe morning sickness admitted to the hospital. Nineteen patients evaluated both on subjective and objective parameters showed that ginger was significantly better than placebo in reducing or eliminating the symptoms of hyperemesis gravidarum.¹⁴

Postoperative nausea

In two randomized double-blind studies, 60 and 120 patients, respectively, received before the operation, a single dose of 10 mg metoclopramide, placebo, or 0.5 g¹⁵ or 1 g¹⁶ powdered ginger, incidence of nausea and vomiting was reduced to similar extents in metoclopramide and ginger and much less when compared to placebo.^{15,16} Also, patients receiving ginger needed fewer postoperative antiemetics.¹⁶ However, another double-blind clinical study concluded that ginger prepared according to the British pharmacopoeia was ineffective in reducing postoperative nausea and vomiting.¹⁷

Drug-induced nausea

Psoralens are taken before undergoing photophoresis. In 11 patients who regularly experienced nausea after ingestion of 8-methoxypsoralen (8-MOP), were treated with three 530 mg capsules of ginger powder taken prior to administration of 8-MOP experienced significantly reduced nausea.¹⁸

In a randomized double-blind placebo-controlled trial with leukemia patients who regularly took prochlorperazine when undergoing chemotherapy, the addition of ginger reduced both the time and the intensity of nausea when taking prochlorperazine alone, although there was no difference in the vomiting.¹⁹

Cisplatin, which is used in cancer chemotherapy, induces nausea, vomiting, and delay in gastric emptying. Experimentally acetone and alcoholic extracts of ginger has been shown to significantly reduce cisplatin-induced nausea in dogs.²⁰ In rats, ginger juice, acetone and 50 percent ethanolic extract have been shown to significantly reverse cisplatin-induced gastric emptying, with the reversal caused by the acetone extract being similar to odansetron that is usually used for this purpose.²¹

NOTES

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LAXATIVES

In Ayurveda it is considered important to maintain a healthy colon for which a number of laxatives are used. In fact, it is considered necessary to have a clean colon before attempting to administer drugs in order for drugs to be effective and especially before attempting the so-called rejuvenation treatment that has its own rules and regulations to be complied with. Thus before the actual process of rejuvenation is started there is a lengthy cleansing process that is undertaken. The most commonly used laxatives are psyllium seed and husk, senna leaves and pods, castor oil and chebulic myrobalan either by itself or together with belleric myrobalan and emblic myrobalan as the three fruit combination of *Terminalia chebula*, *Terminalia belerica*, and *Emblica officinalis*, known as *triphala*.

Cassia angustifolia Vahl (Family: Caesalpiniaceae)

Sanskrit: Markand	Tamil: Nilavari
Hindi: Sonamukhi	English: Indian senna, Tinnevely senna

Cassia angustifolia is a small shrub, which is grown for its leaves and pods that have a cathartic action, the pods having a milder effect than the leaves. The use of *Cassia angustifolia*, indigenous to North Africa, was introduced, by Arabian physicians, into Europe and India.¹ Interaction of Ayurvedic physicians with Unani physicians in medieval times led to the introduction of the plant into the Ayurvedic materia medica. The British introduced the plant for cultivation

sometime in the early nineteenth century. It is cultivated extensively in South India, especially in the Tinnevely (Tirunelveli) district of Tamil Nadu, with estimates of 6,000 tons of senna leaves and pods being produced and exported.² Both leaves and pods are approved in the US and German pharmacopoeia, and several other pharmacopoeias for their laxative action. Apart from its laxative action, it is considered useful in Ayurveda for skin problems.³

Senna's laxative action is due to the anthraquinone glycosides present, mainly sennoside A and B, which are converted by the normal intestinal bacteria into the active constituent rhein anthrone, which stimulates peristalsis and evacuation.⁴

Clinical studies with standardized senna have shown its utility in long-term therapy of habitually constipated patients,⁵ although it is presently recommended only for short-term treatment of constipation. Standardized senna preparation has also been tried in the treatment of constipation immediately after delivery⁶ with average success rate of over 93-96 percent as compared to 51-59 percent with placebo. Mild cramping was seen in those treated with senna as compared to 4 percent with placebo. In this trial there was no evidence of the commonly held view that senna causes diarrhea in breastfed babies when the mother takes senna as laxative.

In combination with psyllium, senna ($6.5 \text{ g} + 1.5 \text{ g} \cdot \text{day}^{-1}$) provided better relief (63 percent) as regards stool frequency and weight when compared to psyllium ($7.2 \text{ g} \cdot \text{day}^{-1}$; 48 percent).⁷ In terminal cancer patients being treated with opioids, senna was found to be as effective as lactulose with similar adverse effect profile but senna was preferred because it was more cost effective.⁸ In children below 15 years of age who were constipated, lactulose was preferred over senna. Twenty-one children in a crossover trial received either lactulose or senna in the first week followed by a wash-out period with no treatment and the alternative treatment in the third week. Normal stools were significantly better with lactulose and the side effects reported by senna were greater.⁹

Senna preparations have been found useful in readying patients for colonoscopy either by exclusively¹⁰ or in addition to the usual lavage.¹¹ One study did not find any advantage in using senna.¹²

Senna pods cause less griping because of lower sennosides content. Other drugs of *Cassia* species like the fruit pulp of *Cassia fistula* are also used as laxative. It is considered a safe drug because of its milder action. This is due to the fact that it contains lower concentration of sennoside A and B, rhein and, other anthraquinones.¹³ Senna is preferred for short-term therapy; long-term use is to be avoided because of the possible mutagenic role of anthraquinones.

***Plantago ovata* Forsk. (Family: Plantaginaceae)**

Sanskrit: Ashwagola	Tamil: Ishappukol, Iskolvirai
Hindi: Isapghul, Isabgol	English: Psyllium or Plantago

Plantago ovata is a stemless, hairy, annual herb found growing in northwest India and cultivated in certain regions of Gujarat, Punjab, and Uttar Pradesh.¹⁴ Indigenous to the Mediterranean region, it is not found in the early texts of Ayurveda, but was later introduced into India. It was first reported in the Ayurvedic text *Vaidyamrta* written in the late eighteenth century by Vaidyaraja Moneswara for the treatment of fever due to diarrhea, and subsequently finds mention in numerous Ayurvedic texts for treatment of intestinal complaints.¹⁵ The seeds are listed in the *Indian Herbal Pharmacopoeia*, 2002, as a bulk forming laxative and antidiarrhoeal agent.¹⁶ The seed husk is also used as a laxative since it separates readily from the seed and is the part which contains the mucilage.

Plantago ovata seeds contain 20-30 percent of mucilage, which is found in the outer seed coat or husk and is composed of arabinoxylans. In addition, the seed contains fixed oil, protein, and small amounts of aucubin—an iridoid glycoside.^{17,18} When the seeds are put in water, the mucilage swells rapidly and takes up several times its volume, the bulk helping peristalsis and evacuation. An unfermented gel component of the seed husk provides lubrication and thereby promotes laxation in humans.¹⁹ The seed husk also contains an active principle-exhibiting acetylcholine-like action.²⁰

A number of clinical studies have confirmed the mild laxative action of psyllium husk in the treatment of chronic constipation, irritable bowel syndrome, and constipation due to diverticulitis. An early open clinical study showed that 13.5 g of psyllium husk improved stool frequency in a 4-week study with 65 patients with an average stool frequency of less than three hard motions per week to 74 percent having a motion every 1-2 days after 4 weeks of treatment.²¹

Another placebo-controlled randomized 8-week study evaluated the effect of psyllium on stool characteristics, colon transit, and anorectal function in chronic idiopathic constipation. After a run-in period of 4 weeks, 22 patients were assigned to one of two groups—11 patients received 5 g psyllium twice a day, and 11 patients received placebo for 8 weeks. Patients maintained a diary to record daily stool frequency, difficulty in defecation, and weekly stool weight. There was significant improvement in stool frequency and stool weight. In addition there was improvement in stool consistency and pain on defecation.²²

Other studies have compared psyllium alone (7.2 g) and a combination of senna and psyllium (1.5 + 6.5 g).²³ Both laxatives improved stool frequency and consistency. Objectively assessed on the basis of stool frequency and weight, laxation was achieved by 63 percent of the combination group, whereas with psyllium alone it was 48 percent. Psyllium has also been compared with lactulose²⁴ and methylcellulose,²⁵ docusate sodium²⁶ and with placebo.²⁷ *Isabgol* husk was effective for the treatment of simple constipation and achieved better stool consistency and fewer side effects when compared to lactulose.²⁴ Psyllium was also found superior to docusate sodium in laxative efficacy.²⁶

In a double-blind crossover study in 26 patients with Irritable Bowel Syndrome (IBS) the effect of ispaghula husk was studied against placebo for 6 weeks.²⁸ Fifty percent of patients receiving ispaghula reported improvement as against 23 percent of patients who were on placebo. Results were better in patients with spastic colitis, little effect being seen in patients with mucous diarrhea. Another study with ispaghula in IBS in combination with *Aegle marmelos* and *Bacopa monnieri* is found under *Aegle marmelos* later in this chapter.

The long-term safety and tolerability of ispaghula husk was also studied in 93 healthy subjects for 52 weeks, the study dosage being 10.5 g per day as long-term treatment of hypercholesterolemia. The majority of adverse effects were of minor nature and of short duration.²⁹ However, the seeds contain allergenic protein that can cause allergic reactions by inhalation to the worker during processing of the product and also to the user when spooning the husk into the glass for consumption.^{18,30} In the carefully prepared seed husk these proteins are absent. Occasionally, abdominal pain has been reported due to distention and flatulence. In cases of intestinal obstruction the use of psyllium is to be avoided.¹⁸

***Ricinus communis* Linn. (Family: Euphorbiaceae)**

Sanskrit: Eranda

Tamil: Ammanaku

Hindi: Erand

English: Castor

Ricinus communis seed oil or castor oil has been used in Ayurveda since the time of Caraka and Sushruta as laxative and for the treatment of rheumatism. The oil is used externally for aching joints. When taken internally for constipation it also helps relieve joint pain and soothe the nervous system (See also Chapter 8 “Anti-inflammatory agents”). Therefore, it is often added to formulations to treat pain, nervous disorders, and menstrual irregularities.³¹ It has been a very commonly used household remedy as a laxative with one or two drops being given even to month-old infants as a laxative till its use fell into disrepute. Castor oil is listed as a stimulant cathartic, lactagogue, and antirheumatic in the *Indian herbal pharmacopoeia*.³²

Castor grows throughout India. Two varieties are known—one with green stem and the other with red stem. The seed contains the highly poisonous lectin, ricin. The oil is cold-pressed below 40°C to prevent the toxic ricin from being carried over to the oil. The seed contains 40-50 percent oil, which is composed up to 80 percent of triricinolein, which is

hydrolyzed in the small intestine to glycerol and ricinoleic acid, which is the laxative agent.³³ Ricinoleic acid increases fluid secretion, releases nitric oxide, increases mucosal permeability and cytotoxicity and disrupts normal intestinal motility.³⁴

The oil is generally used only for a short duration with doses of 10-30 ml being used for adults. There are a number of trials confirming the efficacy of castor oil when given in doses of 15-60 ml and this has been reviewed.³⁵

In a double-blind randomized study, the effectiveness of 0.6 g castor oil in soft gelatin capsules in doses of 1.2, 2.4, and 3.6 g per day was compared with 150 mg senna extract equivalent to 25 mg senosides also in soft gelatin capsules. There were four runs of 1-week duration each and one to two washout periods. The aim of the study was to reach at least five motions per week with the minimum dose possible both for castor oil and for senna. In 15 patients (50 percent) bowel function was normalized with two castor oil capsules (1.2 g) per day, 13 patients required two capsules twice a day (2.4 g) to get the desired effect whereas in two patients the maximum dosage of 3.6 g was needed. With the senna extract (two capsules) 28 patients achieved normalization of bowel function. However, there were no side effects observed with castor oil capsules, whereas seven patients had cramps in the lower abdomen with senna. The stools were always of a soft well-formed mass with castor oil leading to a preference for the castor oil preparation.³⁶

In another study, 75 doctors took part where the trial medication was 1 g castor oil in soft gelatin capsules. A total of 168 patients were observed up to 14 days each. A single intake of three to five capsules once in the morning was recommended. By the end of the observation period, the medication was evaluated by the participating doctors as being “good” to “very good” in 97 percent of patients.³⁷

The safety and usage of castor oil has been extensively reviewed.³⁵ With normal dosages no side effects are observed; however, in sensitive individuals stomach irritation may arise and larger doses can give rise to nausea, vomiting, cramps, and purgation. With dosages of 2-3 ml in more than 200 patients no side effects were seen.³⁵

***Terminalia chebula* Retz. (Family: Combretaceae)**

Latin: *Terminalia reticulata* Roth,
T myrobalanus Koeng

Hindi: Harad, Harar

Sanskrit: Haritaki

Tamil: Kaddukai

English: Chebulic myrobalan

Terminalia chebula is a medium-sized tree found growing throughout India in deciduous forests. The drug consists of the dried rind of mature fruits; the color varies from yellowish brown to brown to black depending upon the source. The drug is approved in the *Indian Herbal Pharmacopoeia*, 2002, as a laxative and astringent.³⁸ The name *haritaki* is derived from the Sanskrit word *hara* (to conquer). The fruits are traditionally considered to be useful for a number of conditions: laxative, stomachic, and tonic.³⁹ The fruits are best known for their laxative properties either alone or in combination known as *triphala* or three fruits—with the fruits of embelic myrobalan or *Emblica officinalis* and belleric myrobalan or *Terminalia bellerica*. Depending upon the dosage, *haritaki* is used as a laxative or to control diarrhea.

The fruit flesh is a rich source of tannins (32-34 percent).³⁹ Major constituents include polyphenolics such as chebulinic acid, chebulagic acid, chebulic acid, gallic acid, and ellagic acid and anthraquinones. Some of the other minor constituents include other polyphenolics like corilagin and galloylglucose, sugars like glucose and sorbitol, flavonoids, triterpene glycosides, amino acids, and some other acids.³⁸

Haritaki is very widely used in Ayurveda as a laxative and has been shown clinically to be useful in cases of simple constipation.⁴⁰ Experimentally, *haritaki* has been shown to significantly increase gastric emptying⁴¹⁻⁴³ comparable to metoclopramide.⁴¹ The laxative principle has variously been suggested to be the oil from the fruit⁴⁴ and an anthraquinone glycoside similar to sennoside A.⁴⁵

In a preliminary trial, 10 patients were admitted as in-patients and underwent hematological, biochemical, and radiological investigations to check for absence of pathology. Symptoms evaluated were frequency of stools, consistency, completeness of evacuation, and

minor disturbances like flatulence, mild abdominal pain, and diminished appetite. Six grams of powder of dried ripe fruits of the big variety of *Terminalia chebula* known as *bari harar* was given at bedtime after meals for 7 days. A daily progress record of the patients was maintained noting changes in symptoms. There was gradual reduction in complaints starting from the day after the start of therapy. At the end of 7 days, incomplete evacuation and reduced frequency had improved in all patients with improvement in consistency, flatulence, and difficulty in evacuation. Total response to the treatment was evaluated as “excellent” in 20 percent and “good” in 80 percent of patients.⁴⁰

Traditionally, the drug *haritaki* is considered to be safe and better than a mother since it does not have adverse effects.⁴⁰ In the clinical trial conducted no side effects were seen.⁴⁰ No toxicity was seen in acute and subacute studies.⁴⁶ Also studied was the effect on liver and renal function parameters and the phagocytic and killing capacity of monocytes and polymorphonuclear cells.⁴⁶ The tannin fraction from *Terminalia chebula* and individual fractions showed antimutagenic effect.⁴⁷

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OTHER LAXATIVE PLANTS

***Picrorhiza kurroa* Royle ex Benth (Family: Scrophulariaceae)**

Sanskrit: Katuka, Katurohini

Tamil: Katukarogini

Hindi: Kutki

Picrorhiza kurroa is best known for its hepatoprotective action (see Chapter 4) because of the extensive scientific work carried out on this aspect, especially on the activity of picroliv, an iridoid glycoside mixture isolated from *Picrorhiza kurroa*. However, in traditional medicine, it is known as a bitter tonic and laxative in small doses, although acting as a cathartic in larger doses.¹

Kutkin, the iridoid glycoside mixture obtained by alcoholic extraction of *P. kurroa* rhizomes, and its two constituent organic acids, cinnamic acid and vanillic acid showed significant choleretic and laxative effects in dogs² and rats.³ Extraction with ethanol leads to enrichment of the laxative effect. The order of activity is picroside I (3.55), kutkoside, kutkin (3), defatted alcoholic extract (2.79), and alcoholic extract (2.31) when compared to crude drug powder.²

One gram of the rhizome powder caused moderate cathartic effect, with a single motion 10 hours after intake. With higher doses of 6 g, drastic purgation was seen.² The powder was better than decoction and cold infusion, probably because of the insolubility of the active constituents in water.

In a comparative study, it was found that *kutlki* was weight/weight 1.5 times more potent than senna and 7.26 times more potent than castor oil.² The safety and tolerability of *kutlki* is covered in Chapter 4 “Hepatoprotective agents.”

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DIARRHEA

Diarrhea is very common in India, especially the ones due to bacterial and protozoal infections. Thus infections like amoebiasis and giardiasis caused by protozoa and bacterial infections caused by *Escherichia coli* and *Vibrio cholerae* are common. It is also a major cause of morbidity and mortality and a large number of plants have been used in Ayurveda for control of diarrhea and dysentery.

***Aegle marmelos* Correa (Family: Rutaceae)**

Sanskrit: Bilva	Tamil: Vilvam
Hindi: Bel	English: Stone Apple, Bengal Quince, Bael

Aegle marmelos is a medium-sized tree and all parts including root, bark, leaves, fruits, and root bark are used as medicine. However, it is the fruit that is most commonly used. The ripe fruit is considered an excellent laxative, whereas the unripe or half-ripe fruit is used for the treatment of chronic diarrhea and dysentery. In India, *Aegle marmelos* was so commonly used by Western doctors during the British rule that it found its way into the British pharmacopoeia. It is official in the *Indian Herbal Pharmacopoeia*, 2002, as an antidiarrheal agent.¹

The fruit contains large quantities of pectin, apart from alkaloids, sterols, and coumarins that have also been isolated. The methanolic² (3-15 mg·animal⁻¹) and 50 percent ethanolic³ extract (100-200 mg·kg⁻¹) of the unripe fruit has been found to exhibit an antidiarrheal effect in small animals.

A few clinical studies have been reported with preparations of unripe fruit. The syrup made from the fruits (*Sharbat-e-Bael*), a *Unani* preparation, which also uses the fruits, was studied at a dose level of

25 ml thrice a day for seven days in a number of cases of acute diarrhea and dysentery.⁴

In an open trial, 5 g of unripe fruit powder was given thrice daily to 25 patients of chronic dysentery for 21 days. Fifty-two percent of the patients were completely cured, 44 percent showed improvement, and 4 percent remained unaffected.⁵

In a study, the effect of unripe fruit on intestinal parasites was tried out clinically and it was concluded that the drug was effective against *Giardia*, *Entamoeba histolytica*, and *Ascaris lumbricoides*.⁶ Twelve grams of the unripe fruit pulp was given in cases of intestinal amoebiasis in three divided doses for 15 days with the response being “excellent” in 81 percent of the cases.⁷ In a randomized double-blind comparative trial to test the efficacy of dried unripe fruit powder in cases of shigellosis (dysentery caused by *Shigella*) it was not found useful, since it did not cause clinical improvement or bacteriological cure as compared to ampicillin.⁸

In another randomized double-blind clinical trial for 6 weeks with 169 patients with irritable bowel syndrome (IBS), a combination of *Aegle marmelos* and *Bacopa monnieri* was evaluated against standard therapy (clidinium bromide, chlordiazepoxide, and isaphagulla) and placebo. The Ayurvedic combination that was tried out in 57 patients was effective in 64.9 percent, whereas the standard therapy in 60 patients was effective in 78.3 percent. There was a 32.7 percent improvement in the placebo group of 52 patients. The Ayurvedic combination was more useful in diarrhea, whereas the standard therapy was useful in the painful form of IBS. However, follow-up for 6 months showed similar rates of relapse for both treatment forms as compared to placebo.⁹

The fruit of *Aegle marmelos* is edible and widely consumed as fruit, despite the hard outer shell of some varieties, or as a fruit drink made with pulp and sugar syrup for its useful action on the stomach,¹⁰ especially in Bengal.

Cyperus rotundus Linn. (Family: Cyperaceae)

Sanskrit: Musta

Tamil: Korai

Hindi: Koreti-jar

English: Nut Grass

Cyperus rotundus is a common weed with aromatic tubers found growing throughout India. The root tuber is commonly used for diarrhea, dysentery, dyspepsia, indigestion, and piles.¹¹ The tubers contain 0.5-0.9 percent of an essential oil containing sesquiterpenes, β -sitosterol, and a flavonol glycoside.¹² The acetone and alcoholic extracts have shown broad spectrum antibacterial activity.¹³

Twenty patients with chronic diarrhea of more than 3 weeks duration, or those in which there was early recurrence after an acute attack, were given 2 g of fine powder of *Cyperus rotundus* root tuber thrice daily along with 50 ml decoction made from 50 g tuber powder given daily for 15 days. The frequency of defecation was controlled by the fifth day of treatment. In addition it helped decrease fat malabsorption and improved lactose intolerance. Forty percent of patients were considered cured, whereas there was improvement in 30 percent.¹⁴ Further work is required to confirm and expand the scope of use.

Cyperus rotundus is generally considered safe and often used to treat stomach complaints in children. In commonly used doses of 1-3 g twice daily no adverse reactions have been reported.¹⁵

***Holarrhena antidysentrica* (Linn.) Wall. (Family: Apocyanaceae)**

Latin: *Holarrhena pubescens*
(Buch.-Ham.) Wallich ex Don

Sanskrit: Kutaja

Tamil: Veppalai

English: Conessi, Kurchee

Hindi: Kurchi

Holarrhena antidysentrica is a small tree found growing throughout India up to 1,200 m elevation. The stem bark is best known as a single drug for the treatment of diarrhea and dysentery, although other parts like the seeds and leaves are also used medicinally. The bark contains up to 4 percent alkaloids, of which conessine has been shown to exhibit potent amoebicidal activity. Other constituents include gum, resin, and triterpenes like lupeol and β -sitosterol.¹⁶

Early pharmacological work on the antiamoebic activity of *kutaja* bark has been summarized.¹⁷ *Kutaja* decoction has also been studied in vitro for its activity against diarrhea producing strains of *Escherichia coli* and found to be effective.¹⁸

In an open trial, 40 patients of amoebiasis and/or giardiasis were treated with 4 g of *kutaja* bark powder in three divided daily doses for 15 days. Cysts were cleared in 70 percent of patients with intestinal amoebiasis (15), whereas all patients showed good clinical improvement. A few patients complained of burning sensation in the abdomen, feet, and head, which was reversible on stopping the drug.¹⁹

Holarrhena antidysenterica is generally considered safe in doses of 2-4 g twice a day.²⁰ However, in the clinical trial on amoebiasis, side effects were burning in the abdomen, feet, and head, which subsided on stopping the drug.¹⁹ In a study to assess side effects in 11 patients, the drug produced subjective symptoms and lowering of blood pressure in three patients.²¹ However, alcoholic extract of *Holarrhena antidysenterica* showed no cellular toxicity when tested against fresh sheep erythrocytes.²²

In a country like India, where amoebiasis and diarrhea are widespread, *kutaja* bark powder or in the form of the preparation known as *kutajarista*, which is well tolerated, in which the drug is extracted by self-generated alcohol, deserves to be further studied.

***Terminalia belerica* Roxb. (Family: Combretaceae)**

Sanskrit: Bibhitaka	Tamil: Tanri
Hindi: Bahera	English: Belleric Myrobalan

Terminalia belerica is a large deciduous tree found growing in forests throughout India. The fruit rind is extensively used in Ayurveda. It is a constituent of the three-fruit combination known as *triphala* that is very commonly used as a laxative and bowel tonic and, depending upon the dosage, also finds application in control of diarrhea.

Bahera is listed in the *Indian Herbal Pharmacopoeia*, 2002, as expectorant, hypolipidemic, and laxative. Depending upon the dose

administered it also finds use in control of diarrhea. It is a rich source (~17 percent) of phenolic acids and tannins from which gallic acid, ellagic acid, ethyl gallate, galloyl glucose, and chebulagic acid have been isolated.²³

In vitro, the alcoholic extract of the fruit also has shown amoebicidal and bactericidal activity against a wide range of bacteria and is considered promising in various forms of dysentery.²⁴ This extract was found to be better than chloramphenicol.

As a follow-up to the promising in vitro results, the drug was evaluated clinically and 25 patients were included in an exploratory study, which took place in five different clinics. Patients were given either 1-2 tablets containing 150 mg per tablet of methanolic extract of *Terminalia belerica* fruit pericarp or placebo thrice a day for 14 days. Doctors were allowed to stop treatment depending upon response and to vary the dose from 1 tablet thrice a day to 2 tablets thrice a day depending upon severity. There were 12 patients on drug and 10 on placebo. All patients on drug responded to therapy and required 12 tablets for recovery. No side effects were observed. Patients on the drug who were found positive for cysts and bacteria became negative, whereas those patients on placebo continued to be positive even after the seventh day.²⁵ Considering the results of this trial it needs to be extended to larger number of patients, especially since *Terminalia belerica* is such a common drug, which would prove useful if the results can be confirmed.

Terminalia belerica is generally regarded as safe in the recommended dosages of 0.75-1.5 gram of the fruit powder taken twice a day.²⁶ Alcoholic extract of *Terminalia belerica* showed no cellular toxicity when tested against fresh sheep erythrocytes.²²

NOTES

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Chapter 4

Hepatoprotective Agents

The liver is the largest solid organ in the body, and it carries out a number of important functions, including metabolism, detoxification, etc. The liver can be damaged by various factors: environmental toxins, such as chemicals; by ingestion of certain drugs, excessive alcohol, other hepatotoxins; and by virus. Thus, the liver is susceptible to a number of disorders because of this multifunctionality and constant exposure to toxins. Liver disorders such as hepatitis, hepatosis, and cirrhosis are a major cause of morbidity. Therefore, agents that can protect the liver from damage and help alleviate an already damaged liver would play an important role in health care, especially since no satisfactory remedy exists in modern allopathic medicine.

PLANT USE IN AYURVEDA

The importance of a healthy liver was realized long ago in India. Plants have been used for centuries in the Indian system of medicine, Ayurveda, for the treatment of liver disorders. In the classical recipes, several plants were combined in a preparation to be used as a remedy. The first recorded medical treatise on Ayurveda—the *Caraka Samhita*—dated to 700 BC describes the use of several multiplant preparations for the treatment of jaundice and other liver disorders.¹

Plant combinations are still the most popular form of plant remedy today: be it the classical formulae based on traditional Ayurvedic texts or the newer proprietary formulations based on Ayurvedic concepts. It is in only in the past few years that a few single-plant

remedies have been introduced in the market. However, single plants have always been commonly used as home remedies—the most popular ones being those based on *Phyllanthus amarus*, *Andrographis paniculata*, *Eclipta alba*, and *Picrorhiza kurroa*.

NOTE

1. *Caraka samhita*, ed. and trans. Sharma PV (vol. II, pp. 261-262, "Chikitsasthanam," chapter XV, verse 132-140) Varanasi: Chaukhambha Orientalia, 1983.

SCIENTIFIC STUDIES

There are approximately 40 hepatoprotective multiplant proprietary products available in the Indian market derived from some 93 plants belonging to 44 families.¹ Of these plants many have been studied individually to determine their chemical composition and to find out their pharmacological action. However, only a few of these plants have been tried out clinically. Most of the trials have been open trials using few patients. In early trials on viral hepatitis, viral markers were not examined. Double-blind placebo-controlled trials have been carried out with only four plants—*Berberis aristata*, *Phyllanthus amarus*, *Picrorhiza kurroa*, and *Tinospora cordifolia*.

A large number of experimental studies have been carried out on individual plants to test for hepatoprotective activity. A survey of literature published between 1986 and 1993 has reviewed the data on 43 plants used in India and elsewhere, of these 24, which included four combinations, showed hepatoprotective activity.² Emerging trends in the field of hepatoprotective plant drugs have been reviewed and several other reviews have been published, apart from a monograph that covers work on Ayurvedic plant drugs for liver diseases.³⁻⁷

Hepatoprotective plants that are interesting because of a combination of factors such as wide usage, traditional use, experimental, and clinical studies are *Andrographis paniculata*, *Boerhaavia diffusa*, *Eclipta alba*, *Picrorhiza kurroa*, *Phyllanthus amarus*, and *Tinospora cordifolia*.

***Andrographis paniculata* (Burm. f.) Wall. ex Nees**
(Family: Acanthaceae)

Sanskrit: Bhunimba, Kirata	Tamil: Nilavembu
Hindi: Kalmegh	English: The Creat

Andrographis paniculata (see Plate 3 in color gallery) is a small herb found in the tropical and subtropical parts of India. The plant is included in the multiplant preparations mentioned in the *Caraka Samhita*.⁸ It has been traditionally used for the following conditions: for sluggish liver; as an antidote to poisons; in cases of colic, dysentery, dyspepsia, fever; and in general debility.⁹ The drug comprises the dried aerial parts of the plant: mostly leaves and stem. It has an intensely bitter taste, which is usually masked by the addition of aromatics. It is also one of the most widely used plants in Ayurvedic formulations for liver disorders, being found in 26 of 40 multiplant preparations.¹⁰ *Andrographis paniculata* or *kalmegh*, the Hindi and Bengali name by which it is commonly known, has the official status in the *Indian Herbal Pharmacopoeia*, 1998, as being a bitter tonic, febrifuge, and a hepatoprotective agent.¹¹

Numerous chemical constituents have been isolated in *kalmegh*, such as diterpene lactones and flavonoids.^{9,11} Andrographolide, a diterpene lactone, which is present up to 1 percent in the plant, has been shown to be the major active hepatoprotective constituent of *Andrographis paniculata*.^{9,11,12} However, the extract from *Andrographis paniculata* is more active than andrographolide suggesting that there are other minor constituents that contribute to the hepatoprotective activity.¹³

The aqueous or alcohol extract of *Andrographis paniculata* has been shown to have hepatoprotective effects in a number of experimental models of liver damage—alcohol, carbon tetrachloride, and benzene hexachloride.¹⁴⁻¹⁷ The aqueous extract prevented necrosis when given to rats for 3 days before the administration of carbon tetrachloride, whereas control rats showed massive necrosis of liver parenchyma cells. Increase in alanine aminotransferase ALT, aspartate

aminotransferase AST, serum bilirubin, and free fatty acids was prevented.¹⁵

In another experiment, such pretreatment resulted in an increase of biliary flow and liver weight, while hexobarbitone sleeping time was reduced, suggesting the induction of microsomal enzymes.¹⁸ The extract also decreased carbon tetrachloride-induced hepatic microsomal lipid peroxidation and inhibited hepatic microsomal enzymes in rats.^{13,19}

Andrographolide, a diterpene lactone, which is the major constituent in the plant has shown hepatoprotective activity against carbon tetrachloride, galactosamine, and paracetamol- and ethanol-induced hepatotoxicity, apart from showing choleretic activity.^{12,20-24}

In an open trial, patients of acute viral hepatitis were given 60 ml of a decoction of *Andrographis paniculata* extract equivalent to 40 g of crude drug in three divided doses, for an average period of 24 days. Patients were assessed both for clinical and biochemical parameters. There was considerable symptomatic relief and statistically significant decrease in serum bilirubin, ALT, AST, and serum alkaline phosphatase, and an increase in protein synthesis as shown by an increase in serum globulin.²⁵

The drug has been used for centuries in India as a household remedy, as it is generally considered safe for use. No adverse effects are reported when administered standard doses; however, large oral doses have been reported to cause gastric discomfort, vomiting, and loss of appetite.¹¹ It is an official status as a drug in the *Indian Herbal Pharmacopoeia*, 1998.¹¹ When given orally, in animals, the minimum lethal dose for andrographolide, neoandrographolide, and deoxydihydroandrographolide is greater than 20 g·kg⁻¹.²⁶ A survey that reviewed the safety and efficacy of *Andrographis paniculata* in upper respiratory disorders reported the drug to be safe and the adverse events being mild and infrequent with few spontaneous reports of adverse events.²⁷

Thus, although there is some evidence for its hepatoprotective activity from experimental studies and a preliminary clinical trial, further clinical work is needed for this much-used medicinal plant to delineate the range of therapeutic efficacy.

***Eclipta alba* (Linn.) Hassk (Family: Asteraceae)**

Latin: *Eclipta erecta* Linn.,
Eclipta prostrata Linn.

Hindi: Bhangra

Sanskrit: Bhringaraja, Kesharaja

Tamil: Karasalanganni

English: Trailing eclipta

Eclipta alba is a small creeping prostrate or sometimes erect plant with white flower heads, it is found throughout India in the moist and wet areas up to an elevation of 2,000 m.²⁸ In Ayurveda, it is considered one of the best plants for the treatment of jaundice. Traditionally the whole plant or its leaves are used. It is also used as a single drug preferably in the fresh state.²⁹ It is one of the most widely used plants in Ayurvedic formulations for the liver with 16 out of 40 preparations in the market containing this plant as one of the ingredients.³⁰ It has an official status as a hepatoprotective agent in the *Indian Herbal Pharmacopoeia*, volume 1 published in 1998.²⁸

Chemically the major constituents are the coumestans—wedelolactone (1.6 percent) and norwedelolactone or demethylwedelolactone, which were recognized as the main active constituents in 1986, 30 years after their first isolation.^{28,31} Other constituents include polyacetylenes, thiophene derivatives, flavonoids, steroids, and triterpenoids.²⁸

Several preparations of the plant, such as powdered aerial parts, fresh leaf juice, aqueous extracts, and alcoholic extracts have been tested for hepatoprotective activity in small animals using a variety of experimental models—carbon tetrachloride, alcohol, acetaminophen, and D-galactosamine.³²⁻³⁵ The plant extract and the coumestans wedelolactone and demethylwedelolactone exhibited antihepatotoxic activity in in vitro assays employing carbon tetrachloride, galactosamine, and phalloidin-induced cytotoxicity in primary cultured rat hepatocytes. In vivo also ethyl acetate fraction protected mice from phalloidin toxicity, no mortality being seen in the group being pretreated with the drug, although the control group showed 70 percent mortality. In addition, ethyl acetate fraction, wedelolactone, and demethylwedelolactone showed significant stimulatory effect on liver cell regeneration.³¹ Wedelolactone has also been shown to be one of

the most potent 5-lipoxygenase inhibitors isolated from plants.³⁶ In vivo *Eclipta alba* has been shown to possess anti-inflammatory activity against carrageenin-induced rat paw edema. It also inhibits the enzyme phospholipase A2 thereby preventing the release of inflammatory prostaglandins by arachidonic acid.³² This combination of anti-inflammatory and hepatoprotective activity makes *Eclipta alba* useful for the treatment of inflammatory liver diseases.

Eclipta alba extract has also been shown to have significant anti-oxidant activity. It is a potent inhibitor of lipid peroxidation and scavenges hydroxy radicals in vitro.³⁷ Extracts of *Eclipta alba* have shown in vitro inactivation of hepatitis B surface antigen (HBsAg) when incubated with HBsAg positive sera isolated from patients.³⁸ However, no further work on this property of *Eclipta alba* has been published.

Clinically, *Eclipta alba* plant powder at a dose level of 50 mg·kg⁻¹ body weight in three divided doses was tried in two open preliminary trials: in 50 children with jaundice and in 20 adults with infective hepatitis.^{39,40} The treatment period varied from 3 to 7 weeks. Clinical response and liver function tests, such as serum bilirubin, alkaline phosphatase, and ALT, were monitored. Testing was continued till patients showed complete biochemical recovery and were followed up for 2-3 months thereafter.

Clinical recovery was observed to be faster than biochemical normalization. Children showed a faster response to the drug when compared to adults; biochemical recovery being seen in 2-3 weeks of therapy. Acute viral hepatitis is for most part a self-limiting disease; however, in countries such as India it can be associated with high morbidity and mortality. Thus, any treatment that can hasten recovery deserves further study.

The aerial parts of *Eclipta alba* are commonly cooked and eaten as a vegetable in South India in order to protect the liver. The alcoholic extract of fresh *Eclipta alba*'s aerial parts did not show any sign of toxicity. When given orally and intraperitoneally in mice, the minimum lethal dose was greater than 2 g·kg⁻¹.³⁴ In the clinical trials no side effects were seen or reported.^{39,40} In a chronic study in mice there was no weight loss, no behavioral changes, and no mortality. In addition, the histopathology of kidney, spleen, and liver of mice showed no significant difference from controls. In tissue culture studies in

vero cells, no cytotoxicity and cytotoxicity was observed when inoculated with *Eclipta alba* extracts.⁴¹

***Picrorhiza kurroa* Royle ex Benth**
(Family: *Scrophulariaceae*)

Sanskrit: Katuka, Katurohini

Tamil: Katukarogini

Hindi: Kutki

Picrorhiza kurroa is a perennial woody herb with grayish brown cylindrical irregularly curved roots 5-10 cm long, found in the North-western Himalayas at an elevation of 2,700-4,500 m. The drug consists of dried rhizome and roots and is widely used in Ayurveda for the treatment of epidemic jaundice.⁴² It is commonly mixed in compound preparations for the liver. The rhizomes have official status as a bitter tonic and for their hepatoprotective action in the *Indian Herbal Pharmacopoeia*, volume I, published in 1998.⁴³

Major chemical constituents of *Picrorhiza kurroa* are iridoid glycosides, picroside I, and kutkoside. Other minor constituents include some iridoid glycosides, such as picroside III, veronicoside, and minecoside, phenol and cucurbitacin glycosides.⁴³

The alcoholic extracts of roots of *Picrorhiza kurroa* were found to be hepatoprotective in number of experimental models. *Picrorhiza kurroa* prevented damage caused to the liver by intraperitoneal administration of carbon tetrachloride, reversing the increase in transaminase levels in rabbits.⁴⁴ It also showed protection against carbon tetrachloride, paracetamol, and aflatoxin damage in rats, at a dose level of 20 mg·kg⁻¹ once a day for 7 days, preventing significant rise of transaminase levels in all three models and restoring Na⁺ K⁺ATPase levels to normal in hepatic injury caused by paracetamol and aflatoxin.⁴⁵ In rats, pretreatment with *Picrorhiza kurroa* ethanolic extract prevented elevation of serum enzymes and glutathione-S-transferase activity by D-galactosamine and carbon tetrachloride, which is attributed to the overall antioxidant effect of the extract.⁴⁶⁻⁴⁸ Among the six plant extracts tested, *Picrorhiza kurroa* was one of the two extracts with the most potent antioxidant activity.⁴⁹ Alcoholic

extract of *Picrorhiza kurroa* has been shown to have a choleric effect in dogs.⁵⁰

Kutkin, the iridoid glycoside mixture from the alcoholic extract of *Picrorhiza kurroa*, has been shown to be the hepatoprotective agent, whereas kutkin-free extracts are not active.⁵¹ Subsequently picroliv, which is a standardized fraction consisting of 55-60 percent of a mixture of two iridoid glycosides picroside 1 and kutkoside I in the ratio 1:1.5, has been studied extensively in a variety of in vivo and ex vivo experimental models: carbon tetrachloride, thioacetamide, alcohol, paracetamol, and galactosamine.⁵²⁻⁵⁸

In addition, picroliv stimulates nucleic acid and protein synthesis in the liver.⁵⁹ In partially hepatectomized rats, rate of recovery in several biochemical markers in regenerating liver was faster.⁶⁰ This was also observed in rats pretreated with picroliv before hepatectomy as compared with control rats.⁶¹

Picroliv showed a dose-dependent choleric effect in conscious rats and anaesthetized guinea pigs.⁶² It also possessed anticholestatic effect against paracetamol-, ethinylestradiol-, carbon tetrachloride-, and thioacetamide-induced cholestasis.⁶²⁻⁶⁴

In an open clinical study, 20 patients with acute hepatocellular jaundice were given 1 g of *Picrorhiza kurroa* root powder thrice daily for a mean period of 26 days. There was significant improvement in serum bilirubin and transaminase levels. It was also tried out in a small group of six chronic patients for an average of 27 days: one patient was considered cured and improvement was seen in the other five patients.⁶⁵ In a double-blind, randomized, placebo-controlled trial, patients with acute viral hepatitis of less than 10 days duration were given 375 mg *Picrorhiza kurroa* powder three times daily for 2 weeks. These patients showed marked clinical improvement in anorexia, malaise, nausea, vomiting, liver size, and tenderness. There was also significant reduction in serum bilirubin and transaminase levels. Bilirubin levels took an average of 75.9 days to fall to 2.5 mg·dl⁻¹ with placebo, while *Picrorhiza kurroa*-treated patients took only 27.4 days to reach the same level. Thus, the drug is found to be useful in therapy of early viral hepatitis.⁶⁶

Picrorhiza kurroa is widely used in India for several indications. In clinical trials on patients with viral hepatitis, no side effects have

been noticed using a dosage of 375 mg thrice daily for 14 days.⁶⁶ It is considered to have a laxative effect at larger dose levels.⁴² It has been reported to have a mild laxative effect at 1 g and drastic purgation at 6 g. Clinical trials have been reported with dose levels of 1g three times a day with no untoward effects.⁶⁷ See also Chapter 3 “Gastrointestinal agents.” In a long-term clinical trial using up to 1 g of root powder for a period of 1 year in patients of bronchial asthma, no side effects were observed, although one patient complained of mild gastric irritation during the last 2 months of the trial. In rats and mice, the alcoholic extract did not affect the weight of spleen, thymus, and adrenals and caused no gastric mucosal damage.⁴²

***Tinospora cordifolia* (Willd.) Miers ex Hook f. & Thoms.
(Family: Menispermaceae)**

Latin: <i>Tinospora glabra</i> (N.Brum.) Merr.	Hindi: Giloe
Sanskrit: Guduchi, Amrita	Tamil: Sindal

Tinospora cordifolia Miers (see Plate 4 in color gallery) is a woody climber found on trees and shrubs throughout the tropical and subtropical parts of India. It grows readily in different soils, the stem attaining a thickness of 6 cm diameter. Usually, however, the diameter is approximately 1 cm.⁶⁸ As a drug, the plant growing on neem (*Azadirachta indica*) trees is considered to be valuable and therefore prized. *Tinospora cordifolia*'s mature stem powder, the aqueous extract, the starch obtained from the stem by repeated washing of crushed stem with water are used in Ayurveda for debility, hepatitis, dyspepsia, jaundice, and other liver disorders.⁶⁹ It is an official drug in the *Indian Herbal Pharmacopoeia*, 1990, for its analgesic and antipyretic activity.⁷⁰

Several classes of compounds have been isolated among them clerodane furanoditerpenes, alkaloids such as jatrorrhizine, palmitine, berberine and tembeterine, steroids, flavonoids, lignans, and a few other compounds.⁷⁰ Anticomplement and immunostimulating activity has been ascribed to TC-1 (a clerodane furano diterpene glycoside), syringin, cordiol, cordioside, and cordifolioside A and B.⁷¹

In acute liver damage caused by carbon tetrachloride, pretreatment for 4 weeks with *Tinospora cordifolia* aqueous extract, prepared by decocting the stems at a dose of $100 \text{ mg} \cdot \text{kg}^{-1}$ body weight, was found to aggravate acute damage. However, it was effective in preventing fibrotic changes in the liver, and it enhanced parenchymal tissue regeneration in albino rats.⁷² In a chronic liver disease model using Kupffer cells, *Tinospora cordifolia* was found to cause significant improvement in Kupffer cell functioning thereby preventing fibrous tissue deposition and tending toward normalization.⁷³ This suggests that the antifibrotic effect is mediated by activation of Kupffer cells.⁷³ An aqueous suspension of alcoholic extract of the stem of *Tinospora cordifolia* was shown to protect against liver damage caused by administration of carbon tetrachloride in mice, rats, and rabbits.⁷⁴ The aqueous extract of *Tinospora cordifolia* also showed significant anti-inflammatory activity in acute and chronic inflammation in rats.⁷⁵

Immune suppression is caused by the development of cholestasis in rats and suggests the need for an immunomodulator such as *Tinospora cordifolia* in the treatment of obstructive jaundice. Thus, treatment with the aqueous extract ($100 \text{ mg} \cdot \text{kg}^{-1}$) of *Tinospora cordifolia* given orally twice daily for 7 days, 4 weeks after the development of cholestasis, resulted in the improvement of cellular immune function as evidenced by normalization of phagocytic activity of macrophages and polymorphonuclear cells, and the intracellular killing capacity of macrophages. Cholestatic rats were also more susceptible to infection; however, when receiving *Tinospora cordifolia* they better resisted infection caused by *Escherichia coli* with 16.67 percent mortality in the treated group as compared to 77.78 percent in the untreated group.⁷⁶

This finding was used in a clinical study where 30 patients undergoing surgery for malignant obstructive jaundice were administered *Tinospora cordifolia* in addition to the conventional treatment of Vitamin K, antibiotics, and biliary drainage.⁷⁷ Thus, only those patients who additionally received $16 \text{ mg} \cdot \text{kg} \cdot \text{day}^{-1}$ of *Tinospora cordifolia* aqueous extract for 3 weeks, after institution of biliary drainage, showed normalization of phagocytic and killing capacity of neutrophils, although in both groups hepatic function was comparable. None of the patients receiving *Tinospora cordifolia* treatment showed septicemia as compared to 50 percent of the patients who were on

conventional treatment alone, although 92.4 percent of the *Tinospora cordifolia*-treated group survived, in contrast to 40 percent postoperative survival in the conventional treatment group.

Tinospora cordifolia is considered safe at the usual dose levels of 3-6 g.⁷⁸ In acute toxicity studies, the stem extract had almost no toxicity; rabbits and albino rats could be administered up to 1.6 g·kg⁻¹ without untoward effects.⁷⁹ In another study on mice and rats, the aqueous extract of stem in a dose range of 50 mg to 1 g·kg⁻¹ was found safe in acute (72 hours) and subacute (4 weeks) studies with no damage to liver and kidney.⁸⁰ The extract was also evaluated on organ function in healthy volunteers for 15 days.⁸⁰

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VIRAL HEPATITIS

Viral hepatitis is a major cause of mortality and morbidity especially in the developing world. Several types of virus have been identified—A, B, C, D, E, and G. Hepatitis A and E, which spread through infected food and water, are usually self-remitting. However, hepatitis B and C, which are transmitted parenterally through infected blood products, through sexual contact, or vertical transmission from mother to child, can become chronic.

Hepatitis B is the most common viral disease in the world with over 300 million chronic carriers. Although a major proportion of patients who contract hepatitis B clear the virus from the blood, a definite proportion of patients go on to become chronic carriers. These carriers serve as a reservoir for further transmission of the disease and they are themselves at a risk of developing liver cirrhosis and/or hepatocellular carcinoma.

Thus, there has been a great deal of interest in testing Indian medicinal plants for their activity against hepatitis B. Of these, the best studied is the plant known as *Phyllanthus amarus* or *bhumyamalaki* in Sanskrit. Earlier literature identifies *bhumyamalaki* as *Phyllanthus niruri* or *Phyllanthus fraternus* and is often reported in literature under this name. However, the plant has now been confirmed to be *Phyllanthus amarus*, with *Phyllanthus niruri* being an American species not found in India.¹

***Phyllanthus amarus* Schum & Thon.**
(Family: *Euphorbiaceae*)

Sanskrit: Bhumlyamalaki,
tamalaki

Tamil: Keelanelli

Hindi: Bhuiavala

Phyllanthus amarus (see Plate 5 in color gallery) is a small herb found throughout the hotter parts of India, especially after the rains. Traditionally, all parts of the plant are used medicinally—leaves, tender aerial parts, and roots. The plant known as *bhummyamalaki* or *tamalaki* in Sanskrit has been known for centuries in the treatment of jaundice. Interestingly the use of the plant *tamalaki* is first mentioned in multiplant preparations for jaundice in *Caraka Samhita*.² It is a commonly used, popular household remedy for the treatment of jaundice. In South India, a bolus of the whole plant is administered with buttermilk. It is traditionally used for jaundice, dyspepsia, colic, and as an appetite stimulant and a diuretic.³ It has been studied extensively, following the discovery that it can bind the hepatitis B virus surface antigen (HBsAg).⁴ The aerial parts of *Phyllanthus amarus* have official status in the *Indian Herbal Pharmacopoeia*, volume II, 1999, for antiviral activity.⁵

Phyllanthus amarus contains lignans, several tannins, flavonoids, sterols, and alkaloids. The lignans phyllanthin and hypophyllanthin have been shown to be hepatoprotective against carbon tetrachloride-induced hepatotoxicity in primary cultured hepatocytes.⁶

The plant has been shown to have an in vitro antiviral activity against hepatitis B.^{4,7} The plant extracts have been shown to inhibit HBs-Anti HBs reaction and inhibit HBV DNA polymerase activity. In cell culture it downregulates HBV mRNA transcription and replication and inhibits enhancer I activity.^{8,9} In woodchucks it has been shown to clear those infected with Woodchuck Hepatitis Virus (WHV) and prolong the mean survival time.¹⁰ The hepatoprotective activity of *Phyllanthus amarus* on carbon tetrachloride and alcohol-induced damage has also been shown.^{11,12}

In a double-blind, placebo-controlled trial, 59 percent of chronic hepatitis B patients became HBsAg negative after ingesting 200 mg powder of aerial parts of *Phyllanthus amarus* three times a day for 1 month, while seroconversion in the placebo group was 4 percent.¹³ In another open trial with 28 chronic HBV carriers, clearance rate of 20 percent was seen in patients who were HBeAg negative, that is those who did not show active replication of the virus.¹⁴ However, in Thailand, a double-blind, placebo-controlled trial using Thai *Phyllanthus amarus* failed to clear HBsAg from asymptomatic carriers.¹⁵

Similarly, seroconversion was not seen in a trial conducted in New Zealand using material from Madras (now Chennai), standardized using geraniin—a hydrolysable tannin—as a marker for standardization.¹⁶

Despite the fact that there have been negative clinical trials, *Phyllanthus amarus* must be considered a plant of potential use for viral hepatitis B. However, further work is required on choice of plant material, method of processing, dosage to be used, and period of treatment, especially because of the presence of ecotypes of *Phyllanthus amarus*.

In acute viral hepatitis, A, B, non-A, and non-B, 4 week-treatment with *Phyllanthus amarus* was compared with Essentiale (as essential phospholipid from soybean oil) and another control group of patients who were treated with vitamins. In acute viral hepatitis B, patients on *Phyllanthus amarus* had significantly faster recovery. *Phyllanthus amarus* also seemed to accelerate the clearance of HBsAg in 86.9 percent of patients of convalescing from acute viral hepatitis B cases in 3 months time, as against 48 percent in the Essentiale-treated group, and 50 percent in controls on vitamins.¹⁷

In an early open trial, in 160 children in the age group of 1-12 years, *Phyllanthus fraternus* (*Phyllanthus amarus*) was found useful in infective hepatitis at a dose level of 50 mg·kg⁻¹ in three divided daily doses for 6 weeks. A total of 101 children who completed the trial were considered cured, although there were 59 dropouts. Clinical response was marked after 2 weeks and no side effects were seen.¹⁸

Phyllanthus amarus has been commonly and widely used in India for a very long time. In dosages commonly used (3-6 g of plant powder twice daily) no adverse reactions have been reported.¹⁹ A 90-day study with mice did not show any mortality or weight loss.²⁰

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OTHER ANTIVIRAL PLANTS

Although a few other Indian plants were found active when tested for activity against hepatitis B, including picroliv from *Picrorhiza kurroa* that was found to bind HBsAg,¹ only *Picrorhiza kurroa* was tested clinically in a double-blind clinical trial on chronic carriers of hepatitis B and found to be inactive.² However, this should be considered only a preliminary result and further work is needed on this. In the trial, patients were divided into four groups and randomly allocated to receive 500 mg of *Phyllanthus amarus*, *Picrorhiza kurroa*, a 1:1 mixture of *Phyllanthus amarus* and *Picrorhiza kurroa*, or a placebo given thrice daily for 3 months. There was a 25-percent clearance in the *Phyllanthus amarus*-treated group, 11.1-percent clearance in the combination group, whereas there was no conversion in the *Picrorhiza kurroa* and placebo groups.

Other single plants that have undergone clinical evaluation are *Berberis aristata* DC. (Family: Berberidaceae) and *Luffa echinata* Roxb. (Family: Cucurbitaceae). In patients of acute viral hepatitis, *Berberis aristata* treatment led to rapid clinical and biochemical improvement.³ In a comparative study of 42 uncomplicated cases of acute viral hepatitis, the effect of Ayurvedic drugs such as *Picrorhiza kurroa* root powder and *Berberis aristata* bark powder at a dose level of 2 g in four divided doses was studied against a placebo. Early clinical and biochemical improvement was seen in drug-treated cases as compared with the placebo group. A better response was seen in *Picrorhiza kurroa*-treated patients as compared to those treated with *Berberis aristata*, whereas clinical improvement was poor in patients on placebo.⁴

In six patients of viral hepatitis, single administration of drops of aqueous extract of *Luffa echinata* dried fruits into the nostrils lead to intense rhinorrhea and to a significant reduction of serum bilirubin

and ALT levels within 2-7 days, and was accompanied by substantial relief in clinical symptoms. The nasal secretions contained total bilirubin ranging from 1.6 to 5.5 mg percent; however, the authors⁵ feel that the possibility that there is nasal absorption of the drug and consequent action on the liver cannot be ruled out.

NOTES

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ASCITES

Boerhaavia diffusa L. (family Nyctaginaceae) has been tried out clinically in cases of ascites due to early liver and peritoneal conditions and has been found to be very beneficial with the drug producing marked diuresis leading in some cases to disappearance of ascites.¹ Experimentally the plant has been shown to have hepatoprotective, diuretic, and anti-inflammatory activity.²⁻⁵ A study of the diuretic and anti-inflammatory activity of different parts of the plant showed that the water-soluble portion of the alcoholic extract of the root and leaf were more active than the whole-plant extract.⁵ It has also been shown that the aqueous extract of the root was more active than the root powder, and it was most active when collected in the month of May.⁶ The plant has official status as a hepatoprotective and diuretic in the *Indian Herbal Pharmacopoeia*,

volume I, 1998⁷ It is a commonly used plant for jaundice, and further studies need to be carried out.

NOTES

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CHRONIC CHOLECYSTITIS

Single plants do not appear to have been tried out in chronic cholecystitis. However, the alkaloid berberine from *Berberis vulgaris*, either as a sulfate or hydrochloride, was shown to be effective in alleviating the clinical symptoms in chronic cholecystitis patients by reducing the bilirubin levels and increasing the gall bladder bile volume.¹ Isolated compounds cannot be considered to be plant drugs, but may point the way to activity in the crude drug or its extract.

Thus, despite the long history of clinical use of plants in Ayurveda for the treatment of liver diseases, few controlled clinical trials have been carried out. Many of the plants have been studied experimentally for hepatoprotective activity, some for choleric and anticholestatic activity, and a few of them for liver cell regeneration

and antiviral activity against the hepatitis B virus. Chemical work to identify active constituents has also been carried out. The result of the scientific studies so far has been the setting off of a differentiation in the pharmacological profile and therefore a change in the way we view these plants. For these plants to acquire a wider usage, further work is required in the universally acceptable standards of their quality, efficacy, and safety.

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Chapter 5

Respiratory Tract Drugs

In modern medicine, respiratory tract drugs include antiallergic drugs, antiasthmatic drugs, and antitussives.¹ In Ayurveda, respiratory problems are considered to arise from poor digestion² and therefore the herbs prescribed in Ayurveda for treatment of respiratory disorders not only improve digestion but also have other useful effects like antiallergic activity and immunostimulant activity. For example, *Piper longum* is a carminative agent that improves digestion, and has antianaphylactic and immunostimulant effects. A large number of herbs have been used to stimulate digestion, reduce the cough reflex, liquefy phlegm, and aid in the removal of phlegm through expectoration. Some of the conditions associated with respiratory tract problems have been classified as *kasa* (cough), *swasa* (dyspnea), and *kasa swasa* (*bronchial asthma*). The most popular home remedies for these conditions include spices, such as ginger, turmeric, black, and long pepper, and common plants, such as *Adhatoda vasica*, *Solanum xanthocarpum*, *Solanum trilobatum*, etc.

NOTES

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PLANTS FOR BRONCHIAL ASTHMA

Bronchial asthma is a chronic allergic condition caused by the sensitivity of the body, especially the respiratory organs, to external allergens, which are often harmless agents such as dust, pollen, temperature, etc. As a result of this hyperreactivity of the bronchial tissues, there is a production of excess phlegm, swelling, and partial blockage of the bronchial passage resulting in wheezing and breathlessness. The Ayurvedic concept and the pathogenesis of the disease are considered to be similar to that in Allopathy and these have been discussed.¹ The Ayurvedic term for bronchial asthma, *tamaka swasa* or less correctly *kasa swasa*, consists of the names of its two major symptoms—cough (*kasa*) and breathlessness (*swasa*). A number of plants recommended by Caraka are still in use today. There are 33 major herbs that have been listed¹ and 22 plants that have been tried out clinically and reviewed.²

Adhatoda vasica Nees (Family: Acanthaceae)

Latin: *Adhatoda zeylanica*
 Medicus, *Justicia adhatoda*
 Linn.

Hindi: Arusa

Sanskrit: Vasa

Tamil: Adhatodai

English: Malabar Nut Tree

Adhatoda vasica is an evergreen perennial shrub found all over India up to an elevation of 600 m.³ The name of the plant is derived from the Tamil (*adu*: goat, *thodathu*: will not touch) because the fetid smell of the leaves keeps goats away. Therefore, it is often used for fencing in villages, as it is safe from grazing animals, and also because it is then readily available for use. Medicinally the use of the plant—leaves, roots, and flowers—has been known for over 2,000 years. The *Caraka Samhita* recommends its use for cough. The leaf of *Adhatoda vasica* is traditionally used in Ayurveda for the treatment of cold, cough, bronchitis, and asthma. It is considered an expectorant, and aids in the liquefying and removal of phlegm.^{3,4} Not

only is it used as a hemostatic agent in bleeding disorders, it also helps in the healing of wounds, in peptic ulcer (see Chapter 3), and in pyorrhea and bleeding gums (see Chapter 14).⁵ The leaf of *Adhatoda vasica* has the official status in the *Indian Herbal Pharmacopoeia*, 2002, as a bronchodilator and an expectorant.⁶

Among the constituents of *Adhatoda vasica* are an essential oil containing limonene, flavonoids, resin, and several alkaloids of which the major alkaloid is vasicine (~1 percent),³ which has been shown to possess bronchodilatory activity.⁷ Vasicinone, a minor alkaloid, has been shown in vitro to be a potent vasodilator.⁸ In vivo vasicinone was found to be as potent a bronchodilator as theophylline and 5,000 times less potent than isoprenaline.⁹

Adhatoda vasica showed antiallergic and antiasthmatic properties in guinea pigs. A fraction containing the minor alkaloid vasicinol and 20 percent vasicine inhibited ovalbumin- and PAF-induced allergic reactions at a dose level of 5 mg per animal by inhalation and 2.5 g·kg⁻¹ by intragastric administration.¹⁰ *Adhatoda vasica* extract of flowers and leaves has been shown in guinea pigs to have an antitussive activity similar to codeine against coughing induced by irritant aerosols.¹¹

A double-blind clinical trial was conducted on “Wintry,” a product containing 25 mg of a mixture of vasicine and vasicinone per tablet, against placebo. One tablet was given thrice a day against the placebo for 4 weeks. An equal number of 30 patients of asthmatic bronchitis received the drug and the placebo, respectively. All patients were given 250 mg amoxicillin for the first week. Out of the 30 patients who received Wintry 21 showed improvement both clinically and on spirometer tests for lung function, 6 of the patients remained unchanged, the condition of 3 patients deteriorated. Of those on placebo, only 4 patients improved, whereas 10 remained unchanged and the condition of 16 patients deteriorated.¹²

The leaves of *Adhatoda vasica* are also commonly used to treat cold and are considered to be effective when administered at the first signs of the infection. Despite the long history of its use, there are no clinical trials to evaluate the full scope of the use of this plant, and this is an urgent requirement.

Despite a long safe history of the use of *Adhatoda vasica* in human beings, there has been concern on the possibility that vasicine exerts an abortifacient effect,⁶ based on evidence from parenteral administration.¹³

An experimental study on rats,¹⁴ on the possible abortive effect of oral administration of 325 mg·kg⁻¹ per day of the leaf extract, produced no abortion in treated animals. Further, after an extensive review of the literature, it was concluded that there is no scientifically valid evidence for potentially harmful effects on human beings, including the effect during pregnancy.¹⁵ Chronic toxicity studies in two species with vasicine hydrochloride at dose levels ranging from 2.5 to 20 mg·kg⁻¹ body weight did not show any toxic effects. There was no difference in the body weight and the mortality of test animals and controls. Histopathology showed no abnormality of major organs.¹⁶ Total extract of the plant, dissolved in water at 2-8 ml·kg⁻¹ for 90 days, showed no toxicity.¹⁷

Albizzia lebbeck Benth. (Family: Mimosaceae)

Sanskrit: Sirish(a)	Tamil: Vagei
Hindi: Siris	English: East Indian Walnut Tree, Siris Tree

Albizzia lebbeck is a large deciduous, spreading tree found all over India, up to an elevation of 1,200 m. The bark, seeds, leaves, and flowers are used for medicinal purposes; however, the bark is considered in the classic literature as the best antidote to both plant and animal poisons. It is used both as a single drug and in combination with other drugs in the form of bark powder or decoction.¹⁸ In Kerala, the bark powder, made into a paste, is rubbed on the body to soothe itching.¹⁹

The stem bark contains 7-11 percent condensed tannins; procyanidin B-2, procyanidin B-5, and procyanidin C-1: (-)-epicatechin; D-catechin; and isomers of leucocyanidin. Also present in the bark are friedelin, β -sitosterol, cardenolide, and anthraquinone glycosides.²⁰⁻²² Three saponins named albizziasaponin A, B, and C have also been isolated.²² The flowers contain, approximately, 4 percent of an essential oil and several saponins lebbekanin A-H.^{20,22}

The flower and bark decoction of *Albizzia lebbeck* has been studied experimentally for its general pharmacological properties, and especially for its antiasthmatic and antiallergic effect.²³ It has shown

immunomodulatory activity and mast-cell stabilization apart from its ability to prevent allergen-induced bronchospasm.

In sensitized guinea pigs, the bark decoction acted as a shield against horse serum antigen,²³ whereas both the bark and the flower decoction protected against histamine-induced bronchospasm. The bark decoction had significant cromoglycate-like activity, such as action on the mast cells, and appeared to inhibit the early process of sensitization and synthesis of reaginic-type antibodies.^{24,25} It reduced the secretion of macrophage migration inhibition factors.²⁵ *Albizzia lebbbeck*, when administered simultaneously with histamine, reduces the release of catecholamine at a dose of $100 \text{ mg} \cdot \text{kg}^{-1}$ up to a maximum effective dose of $200 \text{ mg} \cdot \text{kg}^{-1}$ bodyweight of alcoholic extract.^{26,27} Fractions of stem bark of *Albizzia lebbbeck* also reduced the passive cutaneous anaphylaxis and mast-cell degranulation in rats.²⁸ Hot water and butanol extracts of the bark administered, once daily for 1 week, to mice that were previously immunized by sheep's red blood corpuscles, developed higher antibody titer that was comparable to the standard drug muramyl dipeptide (MDP).²⁹

Bronchial Asthma

A few trials have been conducted with the bark of *Albizzia lebbbeck* in bronchial asthma. A total of 60 patients were given 25 ml of the aqueous decoction, from 100 g of the bark, four times a day for 3 weeks. Excellent results were obtained in cases of not more than 2 years duration; however, in patients with a long history of the disease, the outcome was variable. The decoction was found to relieve difficulty in breathing, reduce cough, and increase the breath holding time, improve the vital capacity and forced respiratory volume in bronchitis. The saponins were considered to be the main active principle behind all these actions.³⁰

In an open trial, 19 patients with bronchial asthma were given 30 ml decoction of *shirish* bark thrice daily for 6 weeks. There was significant fall in eosinophil count and the erythrocyte sedimentation rate ESR and increase in peak expiratory flow rate (PEFR). Nearly all patients experienced symptomatic relief. There was also highly significant effect based on a total of 12 subjective and objective parameters of bronchial asthma such as breathlessness, cough, paroxysmal

attacks of dyspnea, wheezing, rhonchi, pulmonary function tests, etc. assessed in all patients before start of the trial and subsequently four times during and beyond treatment at 15-day intervals.³¹

The flowers have been tried out for tropical pulmonary eosinophilia.³² See later in this chapter. Considering the results obtained so far, further trials need to be carried out with standardized material, controls, and larger patient numbers.

It has been reported that in the experience of Ayurvedic physicians no serious toxicity has been seen clinically.²⁴ In the clinical trial, using the flowers of *shirish*, no side effect or toxicity was seen.³² LD₅₀ in albino rats was found to be 2 g·kg⁻¹ body weight and LD₀ 0.4 g·kg⁻¹. Rats that were given 25 mg·kg⁻¹ of *Albizzia lebbeck* daily for 2 weeks showed no difference, from controls, in body weight, general behavior, and food intake. In addition, the mortality rate was similar in both groups.²⁴

***Boswellia serrata* Roxb. ex Coleb (Family: Burseraceae)**

In Ayurveda, *Boswellia serrata* (see Plate 2 in color gallery) has been used in a number of conditions. In respiratory tract conditions like cough, bronchitis, fever, and asthma it is used either by inhalation of the smoke or as a decoction.^{33,34} When taken internally, it acts as a stimulant expectorant in pulmonary diseases.³⁵

Research has shown that the gum resin of *Boswellia serrata* is useful in a number of inflammatory conditions in which leukotrienes play an important role in the causation and maintenance of diseases, such as inflammatory bowel diseases—Crohn's disease and ulcerative colitis,—rheumatism, asthma, and in the reduction of edema in certain kinds of brain tumor.³⁴ See Chapters 3, 8, and 13. In asthma, leukotrienes are the important mediators of inflammation, which cause bronchoconstriction, mucosal edema, enhance mucous secretion, and raise eosinophil levels. Therefore, leukotrienes have become important targets for potential antiasthmatic drugs.³⁶ The boswellic acids present in *Boswellia serrata* have been shown to inhibit leukotriene synthesis, and therefore are capable of playing a potentially useful role in the management of asthma.

In a double-blind placebo-controlled clinical trial, 80 patients of bronchial asthma were given either 300 mg of gum resin of *Boswellia serrata* or 300 mg lactose as a placebo thrice daily for 6 weeks. In the treated group, the mean duration of the disease was 9-15 years. Seventy percent of the treated group showed improvement in symptoms, such as difficulty in breathing, rhonchii, number of attacks, and lung function tests such as forced vital capacity, etc.,³⁶ leading the authors to believe that further studies, with a standardized product, are required to confirm the initial results obtained.

Boswellia serrata is usually well tolerated; however, it can give rise to gastrointestinal side effects in a small percentage of patients. In the bronchial asthma trial, with 300 mg thrice daily, 2 out of 40 patients complained of stomach pain, nausea, and hyperacidity.³⁶ See also Chapter 3, section “*Boswellia serrata*.”

Curcuma longa Linn. (Family: Zingiberaceae)

Latin: <i>Curcuma domestica</i>	Hindi: Haldi
Valeton	
Sanskrit: Haridra	Tamil: Manjal
English: Turmeric	

Turmeric is a commonly used household remedy for cough and cold, taken mixed in hot milk. It is used, internally, in Ayurveda, to treat asthma, cold, cough, and fever,³⁷ usually along with other herbs and rarely ever alone.³⁸

Curcumin, the main active principle and coloring matter in turmeric, has been shown to have a spasmolytic effect on various spasmogens.³⁹ Extracts of turmeric have been shown to have an antiallergic effect; the ethyl acetate extract being the most active in exerting anti-inflammatory and antiallergic effect.^{40,41} In addition, the curcuminoids are considered to be very effective antiallergic components;⁴⁰ the activity of ethyl acetate extract and curcumin being owing to the inhibition of histamine release.⁴²

Powdered rhizomes of *Curcuma longa* were given in increasing doses from 4 to 32 g daily for 15-45 days to 71 bronchitis patients,

13 bronchiectasis patients, 18 bronchial asthmatic patients, and 12 tropical eosinophilic patients. A significant relief in signs and symptoms was noticed in 11 out of 71 cases of bronchitis, 1 out of 13 cases of bronchiectasis, 5 out of 18 cases of bronchial asthma, and 6 out of 12 cases of tropical eosinophilia.⁴³

Turmeric powder either as such or after frying in ghee—made from butter by heating until most of the water evaporates—was given in a dose of 6-12 g for 15-20 days to patients of asthma with differing “humoral vitiation” according to Ayurvedic criteria based on symptoms such as degree of dyspnea, phlegm, dryness of throat, rales, and ronchi. Sixty percent of the treated patients showed improvement with a decrease in the intensity of cough and dyspnea. In addition, there was a reduction in the amount of sputum. In this trial, the diagnosis was an Ayurvedic diagnosis, and there was variation in the dosage also.³⁸

It would be worthwhile to conduct a trial to check the dosage requirements and the kind of clinical response that can be achieved considering the continued scientific support that turmeric receives from modern investigations.

For details on the safety of turmeric, a commonly used spice in Indian cooking, see Chapter 3. In the trial on patients with bronchial asthma, who were given 12 g·day⁻¹ of turmeric powder, a few patients complained of dryness of mouth and throat, and a mild headache mitigated by the reduction in the dosage or changing the so-called “vehicle,”³⁸ which in Ayurveda, are hot water, milk or milk with clarified butter (ghee), used to aid in the absorption of the drug and in directing it to the required site.

***Ocimum sanctum* Linn. (Family: *Lamiaceae*)**

Latin: <i>Ocimum tenuiflorum</i> Linn.	Hindi: Tulsi
Sanskrit: Tulasi	Tamil: Thulasi
English: Holy basil, Sacred basil	

Sacred to the Hindus, the holy basil is a small herb with an aromatic smell found throughout India and commonly cultivated in gardens and

courtyards. There are two varieties of this herb: one with green stems called *Sri Tulasi* and the other with purple stems known as *Krishna Tulasi*, which is the preferred one in medicine. The leaves of the holy basil are a commonly used household remedy for cough, cold, bronchitis, and asthma. The leaves have the official status in the *Indian Herbal Pharmacopoeia*, 2002, for their expectorant properties.⁴⁴

The leaves contain 0.4-0.8 percent of an essential oil containing eugenol and β -caryophyllene as major constituents.⁴⁴ In addition, the leaves contain tannins (4.6 percent); ursolic acid; several sterols, such as β -sitosterol, campesterol, stigmasterol; flavonoids, such as apigenin, luteolin, and their 7-glucuronides, molludistin, orientin;⁴⁴⁻⁴⁶ and acids, such as gallic acid, caffeic acid, chlorogenic acid, and rosmarinic acid.⁴⁷

Several phenolic compounds, isolated from fresh leaves and stems, exhibited antioxidant activity (e.g. apigenin, rosmarinic acid) and demonstrated COX-1 and COX-2 inhibitory activity (e.g., eugenol, apigenin, rosmarinic acid).⁴⁸ The alcoholic extract of *Ocimum sanctum* leaves was found to be protective against histamine and *Acacia arabica* pollen-induced asthma in guinea pigs in a dose-dependent fashion.⁴⁹ In addition, it acted as an inhibitor against histamine-induced spasm in guinea pig tracheal chain preparation.⁴⁹ A 50-percent alcoholic extract and volatile oil from fresh leaves inhibited histamine and acetyl choline-induced preconvulsive dyspnea in guinea pigs, but the extract from dried leaves did not contain these properties.^{50,51}

All the trials with *Ocimum sanctum* are of preliminary nature and further trials are urgently needed with standardized preparations, larger patient numbers, and better methodology.

Asthma

In an open trial with 20 patients of asthma, 500 mg of *Ocimum sanctum* extract, made into tablets, was given thrice daily for 1 week. Relief was observed, within 3 days, in breathlessness and in vital capacity, but there was no change in the eosinophil count.⁵² In another open trial, the leaves of *Ocimum sanctum* were tried in cases of bronchial asthma and stress-related hypertension, and were found to

be highly effective in these cases. Unfortunately, more details are not available.⁵³

Viral encephalitis

In a preliminary clinical trial, 16 patients with acute viral encephalitis were divided into two groups: one group of ten patients received steroids, whereas the remaining six patients were given dried aqueous extract from 2.5 g of fresh leaves four times daily. The crude extract of *Ocimum sanctum* was found to be more effective than steroids in the treatment of patients with viral encephalitis. In the steroid group two patients dropped out, six died, and two patients had residual paralysis, whereas in the *Ocimum sanctum* group one patient dropped out, one died, three recovered completely, and one had residual paralysis.⁵⁴

The holy basil is generally considered a very safe drug, and many Indians often consume a few leaves as part of their daily ritual.⁵⁵ This habit is often cited as one reason for lower birth rates in men consuming holy basil leaves on a long-term basis, which may have some experimental evidence in the reversible antiandrogenic property of the leaves.⁵⁶ No side effects have been reported in the clinical trials.^{46,52} Constipation was the only side effect, in one trial where doses ranging from 5 to 27 g were taken by 120 patients for 3 months.⁵⁵

Piper longum Linn. (Family: Piperaceae)

Sanskrit: Pippali	Tamil: Tippali
Hindi: Pipli	English: Indian Long Pepper

Piper longum is a slender aromatic climber found throughout the hotter parts of India.⁵⁷ The roots, the stem, and more importantly the fruiting spikes are used for medicinal purposes.⁵⁸ *Piper longum* is a powerful stimulant and has been used for a long time for digestive and respiratory disorders. The fruits and stem are therefore often mixed with the ingredients of a stimulant soup called “*Tippili rasam*”

in South India as a household remedy for cough and bronchial disorders. *Piper longum* has been mentioned in the *Caraka Samhita* as a prophylactic agent in asthma.⁵⁹ It is used in Ayurveda to treat cough, cold, asthma, bronchitis, laryngitis, gas, abdominal distention, and also arthritis and sciatica.^{60,62} *Piper longum* is considered a rejuvenative drug for the lungs, and is used as a milk decoction to treat asthma.⁶⁰ The fruits have the official status in the *Indian Herbal Pharmacopoeia*, 2002, for their antiallergic, antiasthmatic, and hepatoprotective properties.⁵⁷

The fruits contain 1 percent of an essential oil and 4-5 percent of the pungent principle piperine. Other minor components include pipartine and piperlongumine, and a low melting waxy alkaloid N-isobutyldeca-*trans*-2-*trans*-4-dienamide, piperidine alkaloids, a lignan, sesamin, terpenoids, and dihydrostigmasterol.⁵⁷

The petroleum ether extract of the fruits acts as a respiratory stimulant at lower doses. However, with higher doses, it causes convulsions in several species of small animals.^{61,62} Crude extracts as well as the alkaloid pipartine suppressed ciliary movements in the esophagus of frog; pipartine being more active than the aqueous or alcoholic extracts, suggesting that *Piper longum* may act by suppression of cough reflex.⁶³

Piper longum fruit-milk extract reduced effectively passive cutaneous anaphylaxis in rats⁶⁴ and protected guinea pigs against antigen induced bronchospasm. However, there was no significant effect on the total quantity of histamine in various organs—lungs, trachea, and intestines or on the release of histamine on antigenic challenge.⁶⁵ In an experiment using rat lung perfusion in sensitized animals, the milk extract increased the rate of flow.⁶⁶ Piperine blocked the spasms induced by various spasmogens in isolated guinea pig and rabbit intestines, and decreased the rate of respiration.⁶⁷

Bronchial asthma

There is also a special course of treatment in Ayurveda known as *Vardaman pippali* (*vardaman*: increasing; *pippali*: long pepper), which is given as a prophylactic in asthma. During this treatment, long pepper is given in increasing doses to reach a maximum for that

age and then again reduced back to the original dosage. Three clinical studies have been conducted using this kind of regimen.

In a double-blind clinical study, 240 children suffering from bronchial asthma in the age group of neonates to 12 years were given 2-3 courses of the *Piper longum*, each course consisting of a gradually increasing dosage of *Piper longum* starting from a minimum of 1 g to reach a maximum of 30 g, and then a reduction of the dosage to the original dose. There was significant reduction in the frequency and severity of asthmatic attacks, with 80 percent of patients showing improvement, 17 percent no improvement, and 8 percent becoming worse.⁶⁸

In another open study, 20 children (1-12 years) with asthma were administered *Piper longum* fruit powder in a gradually increasing dosage over a period of 5 weeks. Each child below 5 years received the 150 mg fruit powder in capsules, whereas a child above 5 years received 250 mg of the fruit powder in capsules. The dosage was one capsule per day in the first week, two in the second, three in the third, two in the fourth, and one in the fifth week. This regimen significantly reduced the severity and frequency of asthmatic attacks. There was no significant difference in the IgE values in six children. At the end of 1 year, 11 patients showed excellent response, 3 showed moderate response, whereas 3 out of 20 patients failed to show any satisfactory response. Three patients with a history of food allergy were able to consume the offending items after the treatment. There was excellent response to the drug and only one patient complained of nausea.⁶⁹

In a preliminary study, a preparation of *Piper longum* with milk, known as "*Pippali kshira paka*"—made by boiling to dryness 40 g of long pepper in 500 ml of milk and 2 l of water—was given for 4 weeks in three divided daily doses to ten patients with bronchial asthma. The response was evaluated as good to moderate in eight patients.⁷⁰

In another study using "*vardhaman pippali*," in 60 patients with different respiratory disorders, the drug was found to exhibit good efficacy, and was found to be very effective in patients with bronchial asthma.⁷¹

The use of *Piper longum* fruits has been known for a long time, and is well tolerated in the dosages commonly used (250-500 mg thrice a

day).⁷² In the clinical trial on 20 children between the age group of 1 and 12 years, the tolerance to the drug was rated as excellent with only one patient complaining of nausea after the intake of drug.⁶⁹ Nausea was also noted in the trial on patients with bronchial asthma.⁷⁰ Toxicity studies in albino rats employing a milk extract of the fruit boiled in milk at $1 \text{ g} \cdot \text{kg}^{-1}$ did not cause any mortality.⁷² Acute, sub-acute, and chronic toxicity studies showed no adverse effect.⁷²⁻⁷⁴ In the treated animals there was a significant increase in the weight of lung and spleen, as compared to control animals.⁷⁴ No spermatotoxic effect was seen.⁷⁴

***Solanum xanthocarpum* Schrad. & Wendl.**
(Family: *Solanaceae*)

Latin: <i>Solanum surattense</i>	Hindi: Kateli
Burm. f.	
Sanskrit: Kantakari	Tamil: Kandankattiri
English: Yellow-Berried Nightshade	

Solanum xanthocarpum is a very spiny diffuse herb found throughout India. The drug consists of the dried whole plant, including leaves, stem, flowers, fruits, and root, and it has been used medicinally for a number of conditions since the time of Caraka and Sushruta.⁷⁵ However, it is best known for its use in respiratory disorders, helping to expectorate stubborn phlegm in productive cough, bronchitis, and asthma.⁷⁶ The plant is an official drug in the *Indian Herbal Pharmacopoeia* as an expectorant.⁷⁷

The plant contains several steroidal alkaloids—0.2 percent solasodine, solamargine, β -solamargine, solasonine, and sterols, such as cycloartenol, norcarpasterol, cholesterol, and derivatives.⁷⁷

Only a few studies have been carried out and these support the use of the drug in asthma. The glucoalkaloid and fatty acid fractions of *Solanum xanthocarpum* extracts cause liberation of histamine from the lung tissue, suggesting that the beneficial effect of the drug in

bronchial asthma may be due to the removal of histamine from bronchial and lung tissue.^{78,79} The glucoalkaloid and the alcoholic fraction at 2 mg·kg⁻¹ ip also protected against antigen-induced bronchospasm; in sensitized guinea pigs the protection being estimated as 66.6-70.2 percent.⁸⁰ In addition, it has been suggested that the saponins from *Solanum xanthocarpum* may be inducing the formation of anti-allergic substances.⁸¹

The efficacy of *Solanum xanthocarpum* has been tried out in bronchial asthma.⁸²⁻⁸⁶ Starting with a preliminary open study with 11 patients suffering from bronchial asthma and 4 patients suffering from non-specific cough,⁸² the next exploratory study had 60 patients with chronic obstructive airway disease,⁸³ and then *Solanum xanthocarpum* was given to 305 patients with chronic respiratory diseases. There were 250 cases of bronchial asthma, 43 of chronic bronchitis, and 12 cases were suffering from nonspecific unproductive cough. Patients were given whole plant powder in a dose of 1 g, two or three times a day for one month. Fifty percent of the patients showed complete relief of symptoms with no side effects. Complete relief was observed in 55-74 percent of patients with bronchial asthma—all cases of chronic bronchitis—and in seven cases of nonspecific unproductive cough. It was observed that the drug acted like an expectorant in the presence of phlegm, and it acted as an antitussive agent in the case of dry cough.⁸⁴

In the trial of 93 patients with cough (*kasa*), *Solanum xanthocarpum* was found effective in diminishing the intensity of cough and dyspnea in 50 percent of the cases using a total dose level of 60-200g of whole plant or root decoction, given in divided doses over a day for 15-20 days.⁸⁴ The dosages mentioned seemed highly excessive at first, but if taken together with the Hindi summary in the paper where decoction is mentioned and the next paper of the same author where patients were given 60-200 ml of decoction, the 60-200 g probably refers to 60-200 g of decoction and is indicated as such above. A few patients complained of mouth and throat dryness, and a feeling of warmth, which was reduced by lowering the dose.⁸⁵ According to *Selected Medicinal Plants of India*, dosage of *Solanum xanthocarpum* is 1-2 g of drug powder twice daily or 20-60 ml decoction twice daily.⁷⁵

In an open exploratory trial, 44 patients with respiratory problems complaining of cough and dyspnea were given 60-120 ml of the whole plant or root decoction in a divided dosage with added honey for an average of 15-20 days. Diet was controlled and heavy food and salty and sour articles such as pickles were avoided. There was a washout period of 7 days when patients were given glucose capsules. If there was no improvement with the intake of glucose capsules, treatment with the drug decoction was started. Patients were divided into two groups of 21 and 23 based on symptoms as per Ayurvedic criteria. The drug was found to be more useful in the group of patients who had excessive phlegm, with 50 percent of them showing a reduction in the amount of phlegm. The doctors also felt that the root was more effective than the whole plant. The trial serves to give an indication of the utility of the drug and highlights the difficulty in correlating Ayurvedic concepts with modern terms. Side effects were similar to the earlier trial.⁸⁶ There is a need to hold further trials with larger numbers of patients, well-defined parameters, and with a standardized drug.

In an open trial, 16 patients with chronic bronchial asthma were treated with 300 mg tablets of *Solanum xanthocarpum* extract, 2-4 tablets being given thrice daily for 3 months. The improvement was graded as excellent in six, good in three, fair in two, and no improvement in five patients. The drug was evaluated as affording relief to 56 percent of the patients. No side effects were observed in patients even in those with diabetes, hypertension, and coronary heart disease.⁸⁷

In another open trial, the effectiveness of a single dose of 300 mg of powdered whole plant of *Solanum xanthocarpum* or *Solanum trilobatum*—another plant drug commonly used especially in South India—was evaluated against the effectiveness of salbutamol 4 mg or deriphylline 200 mg (combination of theophylline and etioophylline). Pulmonary functions were assessed just before administration and again 2 hours after administration. Treatment with *Solanum xanthocarpum* or *Solanum trilobatum* improved several parameters of pulmonary function significantly, although to a lesser extent when compared to deriphylline or salbutamol. The authors suggest that increased dosages may lead to effects comparable to standard drugs. No side effects were noted, both drugs being well tolerated.⁸⁸

The studies emphasize the need to conduct further studies with a standardized drug to establish the dosage, the mechanism of action, and the usefulness of the drug in asthma.

In clinical trials using *Solanum xanthocarpum*, side effects have generally been observed only in a few patients and have been mild, involving dryness of the mouth and throat, and a feeling of warmth throughout the body, which disappeared on dose reduction.^{85,86} In other studies, the drug was well tolerated and no adverse effects were observed.^{87,88} In albino rats, the hot water extract of seeds showed toxicity at 200 mg·kg⁻¹.^{77,89} In animal studies, the alkaloid solasodine has shown an antispermatogenic activity;⁹⁰ the relevance of these studies for human beings is yet to be established.

***Terminalia belerica* Roxb. (Family: Combretaceae)**

The Sanskrit names of plants are very descriptive: usually evocative of either the appearance of the plant or its uses. Here the name *bibhitaka* or *vibhitaka* indicates that the regular use of this plant keeps one free from diseases. Fruits and oil from the plant have a number of uses: the pulp is analgesic; the unripe fruit is a laxative; and the fruit is a part of the three-fruit combination of *triphala*, which is a bowel tonic and a laxative. The ripe fruit is useful in diarrhea (see Chapter 3). It is also useful in asthma and cough, helping in reducing the bronchial inflammation. The pulp in honey is also used in eye diseases.⁹¹ The fruit pericarp is the official drug in the *Indian Herbal Pharmacopoeia*, 2002, as an expectorant, a hypolipidemic, and a laxative.⁹²

In an open exploratory clinical trial to evaluate the antitussive and antiasthmatic effect of *Terminalia belerica*, 93 patients, ages 1-79 years, were included in the trial after excluding 44 patients with tuberculosis. Among the patients included, 61 were suffering from cough (*kasa*), 12 from dyspnea (*swasa*), and 20 had both cough and dyspnea. The whole fruit, both rind and nut was powdered and administered in doses of 2-6 g thrice a day with water. No period of treatment is mentioned. The symptoms that were assessed were the following: cough (91), dyspnea (51), expectoration (58), pain in chest (29), wheezing (12), temperature (18), loss of weight (25), and

loss of appetite (27). The evaluation revealed that 22 patients showed complete relief in symptoms, 27 had marked relief, 35 moderate relief, and 9 had no relief in symptoms. The clinical impression was that the drug has bronchodilatory, antitussive, and antiasthmatic effects.⁹³

Terminalia belerica is generally considered safe in the doses used clinically. In the clinical trial reported above, the fruit powder was given in a dose of 2-6 g thrice a day with water; no adverse effects were noticed, except for abdominal disturbances, probably due to the laxative effect of the fruit.⁹³

***Tylophora indica* (Burm. f.) Merril (Family: Asclepiadaceae)**

Latin: <i>Tylophora asthmatica</i> Wight & Arn.	Hindi: Antamul
Sanskrit: Arkaparni, Anthrapachaka	Tamil: Nayppalai
English: Emetic swallow-wort, Indian, or Country ipecacuanha	

Tylophora indica is a perennial climber found throughout India, and more commonly in the eastern and southern parts of India, up to an elevation of 900 m. The leaves and roots, with emetic, expectorant, and antidysentric properties, are considered a substitute for ipecacuanha. The use of the plant was initially regional, confined only to areas where the plant grows. Later, interest in the plant grew through the work of Dr. Kotak and Dr. Shivpuri, who showed that consumption of just 3-6 leaves of *Tylophora indica* had prophylactic action lasting for several weeks, and the use of the plant became more widespread. The leaves are used as a household remedy for asthma, bronchitis, and whooping cough.^{94,95}

The leaves contain several alkaloids (0.2-0.4 percent) of which tylophorine (0.1 percent) is the major alkaloid. In addition, there are sterols, α -amyrin, flavonoids, quercetin and kaempferol, tannins, glucose, calcium, salts, etc.^{94,95}

Extracts and alkaloids from the leaves of *Tylophora indica* have been shown to have antiasthmatic, bronchodilatory, anti-inflammatory, antiallergic, and immune suppressive properties. The alcoholic extract and total alkaloids of *Tylophora indica* leaves have shown an antispasmodic effect in isolated tissues⁹⁶ and bronchodilation although inhibiting bronchoconstriction in guinea pig ileum.⁹⁷ Aqueous extract of *Tylophora indica* leaf powder⁹⁸ and tylophorine,⁹⁹ the major alkaloid, have shown an antiallergic effect and have modified the Schutz-Dale reaction in animals. In addition, the aqueous extract caused leucopenia indicating an immunosuppressive effect.⁹⁸ The antiallergic effects have been confirmed by lung perfusion experiments.¹⁰⁰ Tylophorine has also shown significant anti-inflammatory effect in several models of inflammation in rats.¹⁰¹ In vitro, the total alkaloids ($0.1 \mu\text{g}\cdot\text{ml}^{-1}$) prevented the mast-cell degranulation produced by diazoxide at dosages similar to disodium cromoglycate.¹⁰² *Tylophora indica* appears to stimulate phagocytic function^{103,105} although inhibiting the humoral component of the immune system.¹⁰³ *Tylophora* alkaloids also inhibit cellular immune responses^{104,105} when administered at any stage of the immune response.¹⁰⁴

A preliminary clinical study on 56 patients with bronchial asthma and allergic rhinitis showed that there was a marked relief in 40-50 percent of the patients for a few weeks after ingestion of only 3-6 leaves, the dose being 1 fresh green leaf chewed and swallowed per day for 3 days. If the patient improved, no further leaves were given and the condition of the patient was monitored for 12 more weeks. Otherwise, leaf administration was continued for 3 more days, and in recalcitrant cases patients received leaves for 12 days. An initial observation was made that the magnitude of relief in symptoms experienced by the patients was dependent on the intensity of side effects like sore mouth, loss of taste, vomiting, etc.¹⁰⁶ This apparent correspondence between intensity of the side effects and the magnitude of reduction in symptoms was not borne out in subsequent trials.

Following these initial trials, further open and double-blind cross-over trials were performed that too showed significant beneficial effects of *Tylophora indica* in asthma.¹⁰⁷⁻¹⁰⁹

In a double-blind study, 135 cases of bronchial asthma were included and categorized into three groups depending upon the kind of

asthma as seasonal, irregular, and perennial. Patients were randomized into each category and given either drug or placebo in two divided doses for 6 days. Of the 135 patients 71 were treated with dried-leaf powder of *Tylophora indica* and 64 with placebo. The drug consisted of shade-dried and powdered *Tylophora indica* leaf (200 mg), spinach leaf shade-dried and powdered (160 mg), and glucose (40 mg), whereas the placebo contained spinach leaf shade-dried and powdered, and glucose (340 mg) and ipecacuanha (60 mg). Improvement was assessed based on the reduction in signs and symptoms, reduction in the need for bronchodilators and steroids, and improvement in forced expiratory volume (FEV_1) and peak expiratory flow rate (PEFR). On evaluation it was found that the results were not statistically different except in the perennial group where there was a significant response, as compared to the placebo group, at the end of the 2 weeks.¹¹⁰ However, the question arises whether the use of ipecacuanha in the placebo group led to similar results being obtained in the drug and the placebo groups, since ipecacuanha is used as an expectorant.

The efficacy of *Tylophora indica* was evaluated in two cross-over double-blind studies, one against placebo and the other against standard antiasthmatic drug containing ephedrine hydrochloride, theophylline, and phenobarbitone sodium. There was no significant difference in symptoms with the leaf compared to the standard asthmatic drug. In comparison with the placebo, the leaf showed a sustained rise in maximum breathing capacity, vital capacity, peak expiratory flow, and flow rate. There was also a significant reduction in nocturnal dyspnea.¹¹¹

In a trial to evaluate the physiological basis of the therapeutic effect of *Tylophora indica* in bronchial asthma patients, lung function tests, levels of 17-ketosteroids in urine, and absolute eosinophil levels were compared in 18 healthy and 11 bronchial asthma patients before and after the administration of *Tylophora*. Lung function tests included tidal volume, vital capacity, timed vital capacity, compliance, maximum ventilatory volume, and peak expiratory flow rate. Lung function tests were carried out in normal and asthmatic patients immediately after the intake of 10 mg isoprenaline and on the seventh day after two 100 mg capsules of *Tylophora* dried-leaf powder had

been taken twice daily for 6 days. It was found that there was significant improvement in lung function tests in bronchial asthma patients. In addition, 17-ketosteroid levels increased and total eosinophil levels decreased as a result of *Tylophora indica* (*asthmatica*) intake.¹¹²

Allergic rhinitis

In another double-blind cross-over study, 50 allergic rhinitis patients were given either capsules of *Tylophora indica* (250 mg leaf powder) or a placebo (250 mg lactose). Patients received 1 capsule per day for 7 days. This was followed by a washout period of 5 days, then a cross over to the other capsules. Although *Tylophora* produced a significant reduction in the sneezing and nasal obstruction when compared to placebo, there was no significant difference between *Tylophora* and placebo regarding subjective feeling of nasal stuffiness, nasal smear, and response of nasal mucosa to antigen. The authors suggest that a higher dosage of 1 capsule twice a day for a longer period of a fortnight, after which the dose could be reduced, may be more effective.¹¹³

In clinical trials, where a fresh leaf of *Tylophora indica* was chewed, approximately 53-75 percent of patients reported side effects, such as nausea, lasting for a few hours. Sore mouth due to vesicant effect of the leaf and loss of taste for salt was for a longer duration and lasted up to 3-4 days after the last intake of leaf.^{106,107} However, the frequency of side effects came down to 16.3 percent with the intake of the alcoholic extract of *Tylophora indica*. Risk-benefit analysis and the lasting relief obtained by very small doses were considered to compensate for the side effects seen.¹⁰⁸

NOTES

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UPPER-RESPIRATORY TRACT INFECTIONS

The most common upper-respiratory tract infections (URTI) involving the nose, throat, sinuses, and larynx are the so-called common cold and influenza, both of which are viral infections. Common cold is characterized by a stuffy, runny nose, sore throat, headache, and fever. A number of plants have been used in Ayurveda to treat the URTIs; however, these have been little documented. At Banaras Hindu University in Varanasi and elsewhere, plants that stimulate the immune system have been studied for their potential in warding off URTI. Plants that have been experimented with are *Sida rhombifolia*, *Sida vernonicaefolia*, *Sida cordifolia*, and *Abutilon indicum* in combination, *Ocimum sanctum* and *Centella asiatica*. *Centella asiatica* is covered in Chapter 13.

***Andrographis paniculata* (Burm. f.) Wall. ex Nees (Family: Acanthaceae)**

Sanskrit: Bhunimba, Kirata	Tamil: Nilavembu
Hindi: Kalmegh	English: The Creat

Andrographis paniculata (see Plate 3 in color gallery) is a small bitter herb found throughout India. All parts of the plant are used medicinally. The plant is best known as a bitter tonic and febrifuge useful in dysentery, cholera, consumption, influenza, bronchitis, swelling, and skin problems.¹ A tincture of the plant was useful in arresting the progression of the epidemic during outbreaks of influenza in India. It is considered efficacious in intermittent and remittent fevers.² The use of *kalmegh* as a bitter tonic and a hepatoprotective agent has been extensively investigated, as it is one of the most widely used plant in combination formulas for jaundice. See Chapter 4.

Clinical investigation using *Andrographis paniculata* in the prevention and treatment of cold, and the treatment of bronchitis, tonsillitis, and influenza, has been carried out in other parts of the world, notably

in Sweden, where it has been in used for treatment of cold for the past 20 years, and also in Germany, Chile, Russia, and Thailand.

Andrographis paniculata extract and the diterpene lactone, andrographolide, from *Andrographis paniculata* have been the subject of numerous pharmacological investigations. The ethanolic extract³ and andrographolide⁴ have been shown to have antipyretic activity. In addition, andrographolide has been shown to have immunomodulatory,⁵ anti-inflammatory,⁶ and antiallergic⁷ properties. The anti-inflammatory effect is possibly due to inhibition of expression of nitric oxide synthase in macrophages⁸ and PAF-mediated inflammatory response.⁹

Common cold

In a placebo-controlled double-blind study, 1,200 mg of *Andrographis paniculata*'s dried extract containing 4 percent of andrographolides was evaluated against a placebo in 59 patients with common cold. Twelve 100 mg tablets of *Andrographis paniculata* were given to 33 patients, whereas 28 patients received similar-looking placebo tablets containing glucose for 4 days. On day 4, there was a significant reduction in the intensity of sore throat, tiredness, muscular ache, and the intensity of the disease in the drug-treated group but not in the placebo group.¹⁰

In another randomized placebo-controlled double-blind study, 50 patients with initial symptoms of common cold and sinusitis were included in the study and received either *Andrographis paniculata* or similar-looking placebo tablets. The preparation used in the study contained 85 mg of hydro-alcoholic extract standardized for andrographolide and deoxyandrographolide content and was taken in a dose of 4 tablets thrice daily for 5 days. Of the total patients, 67.5 percent in the drug group felt totally recovered compared to 36 percent in the placebo group. In the case of sick leave the drug group took 0.21 days of leave compared to 0.96 days in the placebo group.¹¹

In a pilot double-blind study during winter to evaluate the potential preventive effects in common cold of *Andrographis paniculata*'s dried-extract tablets, 107 children around 18 years of age were recruited. Fifty-four students received two 100 mg tablets of *Andrographis paniculata* for 3 months, which had been standardized to contain 5.6 mg of andrographolide, whereas the other group with

53 students received 2 tablets containing 100 mg glucose. Students were evaluated weekly. There was no difference between the two groups in the number cases with cold in the first 2 months, but after the third month there was a significant decrease in the number of cases with cold in the drug-treated group, with 35 percent catching cold as compared to 62 percent in the placebo group.¹²

In a double-blind placebo-controlled study aimed at evaluating the effectiveness of the extract in reducing signs and symptoms of common cold, 158 patients were recruited who completed the study. The drug group of 79 patients received 1,200 mg·day⁻¹ of *Andrographis paniculata* herb extract standardized to contain a minimum of 5 mg andrographolide and deoxyandrographolide, that is, four 100 mg tablets three times a day, and the placebo group with 79 patients received an equivalent amount of placebo tablets for a period of 5 days. After the second day of treatment, there was a significant decrease in the severity of exhaustion, sleeplessness, sore throat, and nasal secretion, whereas on day 4, there was a significant decrease in all symptoms in the *Andrographis paniculata* group—headache, earache, phlegm, and frequency and intensity of cough.¹³

Two other double-blind placebo-controlled trials, a pilot study with 46 patients and a phase-III study involving 179 patients with uncomplicated URTI, found that throat symptoms showed the most significant improvement.¹⁴

In a randomized double-blind comparative study in 152 adult patients with pharyngotonsillitis, the efficacy of the powdered leaves of *Andrographis paniculata* encapsulated in 250 mg and 500 mg capsules was evaluated against 325 mg paracetamol capsules in reducing the incidence of sore throat and fever. Patients were randomized and asked to take 3 capsules four times a day. After 3 days of treatment, the crude drug at 6 g·day⁻¹ was found as effective as paracetamol in control of fever and sore throat after 7 days; clinical effects were not different in the three groups.¹⁵ In an open study, treatment with standardized *Andrographis paniculata* showed reduction, within 48 hours, in the incidence of fever occurring with common cold.¹⁶

In two randomized double-blind-controlled clinical studies—a pilot study and a second study—*Andrographis paniculata* was evaluated against amantidine in an epidemic of influenza in Volgograd.

The pilot study involved 540 patients: 71 patients were on a combination drug Kan Jang consisting of 88.8 mg of *Andrographis paniculata* and 10 mg of *Eleutherococcus senticosus*, whereas the control group was on an antiviral drug amantidine, paracetamol, and vitamin C. The Kan Jang therapy significantly reduced the occurrence of fever and clinical symptoms, such as headache, myalgia, and conjunctivitis, postinfluenza complications, and the number of days taken as sick leave was also reduced to 30.1 percent and 31.43 percent compared to 67.8 and 70.97 percent in the control group of the pilot and second study.¹⁷

The results of several trials on URTI in which a standardized extract of *Andrographis paniculata* has been used, with one exception, has been reviewed for safety and efficacy, which shows that there are only mild and infrequent reports of adverse events.¹⁸ For other details see the Chapter 4 monograph "*Andrographis paniculata*."

NOTES

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OTHER PLANTS

In an open exploratory study, *Ocimum sanctum* was taken regularly by patients suffering from recurrent cold and URTI in the form of fresh leaves or decoction. It was found to prevent recurrent attacks presumably by stimulating the immune system. Similarly, in a study of 74 children subject to recurrent URTI, a four-herb combination of *Sida cordifolia*, *Abutilon indicum*, *Sida rhombifolia*, and *Sida*

veronicaefolia was found to have a highly significant effect in reducing the frequency of attacks after 12 months of intake, when compared to the pretreatment period.¹

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TROPICAL PULMONARY EOSINOPHILIA

Tropical pulmonary eosinophilia is a tropical disease found in India. It is characterized by cough, breathlessness, and high eosinophil levels of more than $2,000 \cdot \text{cu} \cdot \text{mm}^{-1}$.^{1,2}

Albizzia lebbbeck Benth. (Family: Mimosaceae)

In an open trial with 35 cases of tropical pulmonary eosinophilia (TPE), 17 patients were treated with 200 mg *Albizzia lebbbeck* (*shirish*) flower twice daily for 6 weeks, with 82 percent showing excellent results, 12 percent good, and 6 percent showing poor response. No side effects or toxicity were observed.¹

Ocimum sanctum Linn. (Family: Laminaceae)

A double-blind comparative clinical trial of *Ocimum sanctum* with diethyl carbamazine was conducted on 48 children with TPE. Patients were randomized into two groups—one receiving $200 \text{ mg} \cdot \text{kg} \cdot \text{day}^{-1}$ of *Ocimum sanctum* or $10 \text{ mg} \cdot \text{kg} \cdot \text{day}^{-1}$ diethyl carbamazine in three or four divided doses for 4 weeks. Both drugs were filled in identical capsules and the trial was conducted in a double-blind manner. *Ocimum sanctum* was found as effective as diethyl carbamazine in effecting clinical improvement and reduction of blood eosinophil levels, apart from producing similar improvement in radiological findings. Change in eosinophil levels was noticed in the second week of therapy when patients were examined and improvement in

eosinophil levels continued when repeat measurements were carried out in the fourth week.^{2,3}

***Terminalia belerica* Roxb. (Family: Combretaceae)**

In a comparative trial of 37 children with cough, breathlessness, fever, chest pain, malaise, an eosinophil count of $2,000 \cdot \text{cu} \cdot \text{mm}^{-1}$, and more than 20 percent differential eosinophil count, 27 patients were given $20 \text{ mg} \cdot \text{kg}^{-1}$ body weight of the kernel powder of *Terminalia belerica* in three divided doses, whereas ten patients received diethyl carbamazine (DEC) as a control drug. There was a significant reduction in the blood eosinophil count after 15 days that was completely normal after 4 weeks of treatment in comparison with DEC. Six-month follow-up showed that there were no relapses in the *Terminalia belerica* group, but there were relapses in the DEC-treated group.³

NOTES

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Chapter 6

Cardiovascular Drugs

Disorders of the cardiovascular system (heart, blood vessels, and blood circulation) are a major cause of morbidity and mortality in the world. With changing lifestyles and diet, as also with increased stress and pollution, cardiovascular diseases are reaching epidemic proportions not only in the developed world but also in the developing world. Plants have been used in Ayurveda for the treatment of heart disease or *Hrdroga*, as it is known in Sanskrit, both in the form of a single drug and in combination with other plants. There have been several plants that have been listed in ancient treatises as useful for heart problems since the time of Caraka and Sushruta—authors of the first Ayurvedic texts. Several reviews have been published considering the importance of the area. These include plants found useful in cardiovascular conditions,^{1,2} which have been grouped under four categories depending upon their activity, such as cardioprotective plants that help in the management of ischemia and angina,³ antiplatelet plants,⁴ antihyperlipidemic plants,⁵ and antihypertensive plants.^{6,7} Many of these plants can be included in more than one category.

NOTES

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CARDIOPROTECTIVE PLANTS

Of the few plants that have been studied, the best investigated is *Terminalia arjuna*, which has evoked considerable interest since the published report of a poor barber with ischemic heart disease (insufficient blood supply to the heart), owing to a heart block, who was relieved of his symptoms and was able to start work again. The barber was advised a milk decoction of *Terminalia arjuna* bark twice a day that relieved him of his symptoms.¹ Angina pectoris is characterized by pain in the chest due to coronary artery disease (CAD) or narrowing of the coronary arteries by deposition of fatty plaques on the wall of the arteries. In Ayurveda, factors causing heart disease and treatments for it have been described in the *Caraka Samhita*. The treatment of pain has also been included in it.² Acute chest pain with breathlessness is described in the *Sushruta Samhita*.³ However, the different kinds of pain because of heart disease have been described in the *Astanga Hridayam* of Vagbhata, who also first advocated the use of *Terminalia arjuna*.⁴

***Terminalia arjuna* (Roxb.) Wight & Arn. (Family: Combretaceae)**

Sanskrit: Arjuna

Tamil: Vellamatta

Hindi: Arjuna

Terminalia arjuna (see Plate 6 in color gallery) is a large evergreen tree found throughout India, especially near waterways. It is also grown for its shade. The smooth pink-gray stem bark has been used

as a medicine for hundreds of years since 700 BC. Mentioned in the *Caraka* and *Sushruta Samhita* for the treatment of skin conditions, ulcers, fractures, uterine problems, and urinary disorders,⁵ the use of *Terminalia arjuna* in heart diseases was mentioned for the first time in the *Astanga Hrdayam* of Vagbhata.⁶ Its use as a cardiotonic in heart problems, especially in the form of a milk decoction, was advocated by another well-known physician of ancient times known as Cakra-datta or Cakrapanidatta.⁷

Constituents isolated from *Terminalia arjuna* bark include the following components: tannins; several triterpenoid genins and glycosides, including arjunic acid, arjunolic acid, terminic acid, arjungenin, arjunolitin, arjunetin, arjunglycosides I, II, III and friedelin; flavonoids, such as arjunolone and baicalein; phenolic acids, such as ellagic acid; leucoanthocyanidins, for example leucocyanidin and leucodelphinidin; phytosterols (β -sitosterol); and large amounts of calcium salts.^{5,8}

Early pharmacological studies using the total extract of *Terminalia arjuna* showed cardiotonic activity, increasing the force of contraction in frogs⁹ and in dogs.¹⁰ In a study to investigate the mechanism of action, it was found that the aqueous portion of the alcoholic extract exhibited a lowering of blood pressure and heart rate (bradycardia), which was centrally mediated,¹¹ whereas another study showed that *Terminalia arjuna* had a depressant action at higher concentration because of its peripheral action.¹² A significant positive inotropic effect was also shown in rat atria by the aqueous extract,¹³ which has been attributed to the release of noradrenaline from the sympathetic nerve endings, that is by an action on β_1 -adrenoreceptors, although the extract caused a relaxation of vascular smooth muscle, which was not mediated by β_2 adrenoreceptors.¹⁴ Depending upon the solvent used for extraction, the extract is enriched in compounds possessing either positive or negative inotropic action.^{11,13,14}

In isoproterenol ischemia in rats, *Terminalia arjuna* showed prostaglandin E_2 (PGE_2)-like activity inducing coronary vasodilation and hypotension.¹⁵ The aqueous extract also enhanced coronary flow in isolated perfused rabbit heart preparation.¹⁶ Powdered bark has been shown in rats to prevent oxidative stress associated with ischemic reperfusion injury.¹⁷ In addition, arjunolic acid, a triterpene from the bark, has been shown to exert a protective effect against damage

caused by isoproterenol-induced myocardial necrosis.¹⁸ *Terminalia arjuna* also has potent antioxidant activity¹⁹ and has a favorable effect on coronary risk factors such as hyperlipidemia, lowering cholesterol levels in rabbits fed a high-fat diet.²⁰⁻²⁵ The lipid-lowering effect has been shown to occur through inhibition of cholesterol biosynthesis in the liver and increased excretion of bile acid. There is also an increased activity of the enzyme responsible for lipid metabolism in the body—plasma lecithin, cholesterol acyltransferase activity, and stimulation of the receptor responsible for the destruction of low-density lipoprotein.²⁶ *Terminalia arjuna* bark 50 percent methanolic extract, at a dose level of 250 and 500 mg·kg⁻¹, reversed the abnormal platelet adhesiveness and the incidence of ECG abnormalities in hypercholesterolemic rabbits,²⁷ and at the same dose level improved the endothelial function.²⁸

A number of studies have investigated the use of *Terminalia arjuna*; most of them have been in the area of angina and ischemic heart disease, one in congestive heart failure, a few cases of ventricular arrhythmias, in its antioxidant capacity and in the control of hyperlipidemia. One of the first studies that triggered interest in the use of *Terminalia arjuna* was conducted in 1951.²⁹

Angina pectoris

In an open trial, 25 patients with angina pectoris were given 500 mg of *Terminalia arjuna* bark extract twice a day in addition to their usual antianginal drugs for 3 months. When evaluated at the end of 1 and 3 months, respectively, it was found that the exercise tolerance increased and the treadmill grading had significantly improved. There was, however, no reduction in the consumption of antianginal drugs and the drug was well tolerated and no side effects were observed.³⁰ Details are not available regarding the extraction solvent used for preparation of the bark extract.

In another open trial with 15 stable and 5 unstable angina patients, *Terminalia arjuna* was given for 3 months, at the end of which, in the stable angina group, there was a significant improvement in angina, decrease in blood pressure, and improvement in exercise tolerance increased as indicated by the delay in onset of angina on a treadmill test. In unstable angina patients, there was only an insignificant

change in anginal frequency. No adverse effects were seen on liver and kidney functions.³¹

In another open trial, 29 patients with angina pectoris were administered 600 mg of *Terminalia arjuna* bark powder. In 17 Tread Mill Test (TMT) positive cases, improvement seen was evaluated as 20.3, 57, and 67 percent reduction of symptoms after 20, 40, and 60 days of treatment, whereas in TMT negative cases greater improvement was seen with 30.4, 47, and 68 percent reduction of symptoms, respectively.³²

In a double-blind placebo-controlled cross-over study, 58 male patients with chronic stable angina NYHA class II-III, who showed provokable ischemia on exercise, were given 500 mg of *Terminalia arjuna* 90 percent alcohol extract 8 hourly, isosorbide nitrate 40 mg daily, or a matching placebo for 1 week each after a wash-out period of 3 days in a randomized double-blind cross-over fashion. All patients were evaluated clinically at the end of each week of therapy apart from biochemical and treadmill exercise evaluation. Patients on *Terminalia arjuna* extract showed improvement both in clinical parameters and exercise tolerance, which was similar to isosorbide mononitrate when compared to placebo.³³

Congestive heart failure

Properly evaluated plants can be useful in the long-term treatment of chronic heart failure (inadequate heart function causing insufficient supply of oxygen and nutrients to the lungs and extremities). In an early study ten patients with congestive heart failure, who were classified as being in NYHA Class I (one patient), Class II (five patients), and Class III (four patients), were given 4 g of powdered *Terminalia arjuna* bark twice a day before food for 1 month, which caused a significant diuresis ($p < 0.01$). All patients showed improvement in their functional class, breathlessness, and overall feeling of well-being and comfort. In addition, there was a fall in both systolic and diastolic blood pressure.³⁴

In a double-blind placebo-controlled study, 12 patients with severe refractory heart failure, NYHA Class IV, were given either 500 mg of *Terminalia arjuna* bark extract 8 hourly or a matching placebo for 2 weeks each as an adjuvant, in addition to the patients' intake of digoxin, diuretics, ACE-inhibitors, vasodilators, and potassium

supplementation. After 2 weeks there was a wash-out period for 2 weeks, before the cross-over preparation was administered. All patients experienced breathlessness during rest period or after minimal activity. Baseline evaluation was carried out for both clinical and laboratory parameters, in addition to an echocardiogram at the start of the trial, after *Terminalia arjuna* and placebo treatment. There was an improvement in dyspnea, fatigue, edema, and the walking distance when patients were on *arjuna* therapy. At the end of 4 months nine patients had improved to Class II, whereas three patients had improved to Class III. In the second open phase of the trial all patients were continued on *arjuna* therapy (500 mg every 8 hours) for about 2 years in addition to their other drugs (flexible diuretic, vasodilator, and digitalis), and patients continued to show improvement in signs and symptoms, exercise tolerance, NYHA class, and quality of life.³⁵

Coronary artery disease

In two cases of ventricular premature contractions associated with coronary artery disease, *Terminalia arjuna* powder 500 mg was given thrice a day, and ventricular premature contractions disappeared in both cases.³⁶

In an open study, ten patients of postmyocardial infarction angina (post-heart attack chest pain) and two patients of ischemic cardiomyopathy (disease of the heart muscle causing weakened force of contraction) were treated with 500 mg of *Terminalia arjuna* stem bark powder 8-hourly for 3 months in addition to the conventional treatment of nitrates, aspirin, and/or calcium channel blockers. Another group of 12 patients with postmyocardial infarction angina, who were only on conventional treatment, served as controls. Both groups showed a significant reduction in anginal frequency; however, only the *Terminalia arjuna* group showed a significant reduction in left ventricular ejection fraction and reduction in left ventricular mass, as shown by echocardiogram. In addition, two patients with cardiomyopathy showed improvement in coronary heart failure from NYHA Class III to Class I. No side effects on the kidney, liver, and blood were seen.³⁷

Lipid lowering in coronary heart disease

In an open trial, 51 cases with coronary heart disease (CHD) were treated with 500 mg of *Terminalia arjuna* bark powder filled in capsules and given 2 capsules twice daily with milk for 4 months. There was a significant regulation of blood pressure and lipid profile in these patients. Patients got considerable symptomatic relief with improvement in breathlessness, palpitation, and chest pain after 1 month of treatment and there was significant normalization at 4 months.³⁸

In a randomized open trial, 105 patients with CHD were matched for age and disease status and then randomized into three groups. One group received placebo capsules, one group received 400 IU of vitamin E, and the third group received 500 mg capsules of *Arjuna* bark powder. Lipid and lipid peroxide levels were determined after 30 days of intake. There was no significant change in lipid levels in groups receiving placebo and Vitamin E, whereas in the *arjuna* group there was a significant decrease in total cholesterol and LDL cholesterol. In addition, there was a significant reduction in lipid peroxide levels in both vitamin E and *arjuna* groups.³⁹

Terminalia arjuna is well tolerated in the usual dosages of 1-2 g used in clinical trials and considered optimum for the treatment of coronary artery disease (CAD).^{30, 40} Side effects seen are mild—gas tritis, headache, constipation, abdominal discomfort, body ache, nausea, and insomnia—and only in a few patients.^{33,35} No organ toxicity in liver and kidney,³⁷ and no metabolic toxicity has been reported in patients taking *Terminalia arjuna* for 24 months.³⁵ In vitro studies have shown that methanol and acetone extracts of *Terminalia arjuna* show an antimutagenic activity.⁴¹

***Inula racemosa* Hook f. (Family: Asteraceae)**

Sanskrit: Pushkara

Hindi: Pushkaramoola,
pokharmoola

Inula racemosa is a tall stout herb growing up to 1.5 m in the north-western Himalayas from 1,500 to 4,200 m elevation.⁴² The roots are

prized in Ayurveda for their expectorant action in cough and also in breathlessness and chest pain. It is described in the *Caraka Samhita* as the best drug for precordial pain⁴³ and also mentioned in several other formulae, both as a single drug and in combination with other drugs for the treatment of heart disease. It is also used internally for the treatment of tuberculosis and externally for skin problems.

Roots of *Inula racemosa* contain 10 percent inulin and 1.3 percent of an essential oil, which contains several lactones, chiefly alantolactone and isoalantolactone.^{42,44}

Inula racemosa has been shown to have a protective effect on experimental myocardial infarction in rats when compared to a control group.⁴⁵ In addition, it has also been shown to have a negative inotropic and chronotropic effect in frog heart.⁴⁶

Based on the high regard accorded to *Inula racemosa* by Caraka in relieving chest pain, it was tried out in a small number of patients with ischemic heart disease complaining of chest pain and ST-segment depression shown in the ECG on exertion. In an open study, nine patients with ischemic heart disease were treated with 3 g of *Inula racemosa* root powder taken 90 minutes before testing. At this dosage it prevented postexercise ST depression in all cases, leading the authors to conclude that the results were comparable to nitroglycerine with enhanced improvement seen with *Inula racemosa*.⁴⁷

In an earlier trial with *Commiphora mukul* in cases of ischemic heart disease, it was found that patients continued to have precordial pain for periods ranging from 3 to 9 months, despite the intake of guggul, and requiring the additional use of nitroglycerine to control pain.⁴⁸ Therefore, *Inula racemosa*, which is considered the drug of choice to control chest pain, was added. In an initial trial, a combination of *Inula racemosa* with *Commiphora mukul* gum in the ratio of 1:1 was tried on 50 patients with ischemic heart disease at 6 g per day in three divided doses for 4 months. At the end of the trial period, five patients had recovered and had no precordial pain, and the serum cholesterol and ECG were within normal limits. A total of 40 patients showed varying degrees of improvement such as reduction in precordial pain and ECG or serum cholesterol levels although five patients did not show any improvement at all. A longer treatment period was expected to yield the desired results.⁴⁹

Thus, two studies have been published by the same institution—one in which 150 patients⁵⁰ were enrolled and the other with 200 patients.⁵¹ All patients had precordial pain relieved with nitroglycerine and showed breathlessness and changes in the ST-segment depression and T-wave in the ECG after exercise, which is characteristic of myocardial ischemia. Patients were recruited for the trial and given 6-8 g of the 1:1 combination of the drug for a period of 6 months. Cholesterol, triglycerides, and total lipids showed significant fall from the first month onwards.⁵⁰ At the end of the trial period, of the 200 patients, 25 percent (52 out of 200) had a normal ECG, 59 percent showed improvement in ECG, 25 percent (50 out of 200) had no precordial pain, and 69.2 percent patients (110 out of 159) had no dyspnea.⁵¹

To further improve patient comfort, two further combinations were tried out. In the first combination *Bacopa monnieri* plant juice, which has an anxiolytic effect, made from an equal quantity by weight was added to equal amounts of the powders of *Inula racemosa* and *Commiphora mukul* and made into 500 mg pills; 12 such pills were given to 50 patients in divided doses for a period of 6 months and ECG taken for 45 patients. After 6 months, 8 out of 45 patients had no precordial pain and both ECG and lipid levels were normal; 60 percent (30 out of 45) of the patients showed improvement in chest pain, in ECG, and serum lipid levels, 8 out of 45 patients improved with relief only in precordial pain but not in lipid levels or ECG, whereas two patients showed no improvement.⁵²

In the second combination, in addition to *Inula racemosa* and *Commiphora mukul*, *Centella asiatica* and *Hypericum perforatum* were added to allay anxiety and depression in 406 patients with one or more risk factors for CHD. The formulation consisted of 500 mg of total extracts per capsule combined in the following ratio: each 20 mg of the combination contained *Inula racemosa* root extract—3 mg·kg⁻¹; the gum resin of *Commiphora mukul*—7 mg·kg⁻¹; *Centella asiatica* whole plant extract—8 mg·kg⁻¹; and *Hypericum perforatum* leaf extract—2 mg·kg⁻¹. The drug combination was administered in a dose of 20 mg·kg⁻¹ in divided doses for 6 months. A control group consisting of 57 males and 28 females were kept on placebo. The drug-treated group showed significant improvement in nervousness,

sleeplessness, tremors, irritability, and fatigue. In addition, there was a decrease in both diastolic and systolic blood pressure, correction in total cholesterol, and increase in HDL-cholesterol ratio in the treated group, but not in the placebo group.⁵³

Larger doses of *Inula racemosa* have a laxative effect.⁵⁴ In a 1:1 combination with *Commiphora mukul* it showed no adverse effect when given to 250 patients with CHD to assess the effect on body composition.⁵⁵

NOTES

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HYPOLIPIDEMIC PLANTS

Lipid levels are considered to be a risk factor for several diseases, including heart problems. Over 50 plants are used in Ayurveda to lower lipid levels.¹ The etiopathology of obesity and associated lipid disorders have been described in a very comprehensive manner in the *Sushruta Samhita*,² and its parallel to modern theories of the development of atherosclerosis was noticed by Dr. Satyavati and Dr. Dwarkanath in the 1960s.³

Commiphora wightii (Arn.) Bhandari **(Family: *Burseraceae*)**

Latin: *Commiphora mukul* Engl, *Balsamodendron mukul* Hook ex Stocks

Sanskrit: Guggul, Devadhoopa

Hindi: Guggulu, guggul

Tamil: Maishaki Gukkal

English: Indian Bdellium

Commiphora wightii, better known in the literature as *Commiphora mukul* (see Plate 7 in color gallery), is a small to medium-sized tree found in the arid regions of India. It is cultivated in Rajasthan and Gujarat. The tree has a papery bark, and when an incision is made in the bark, a thin yellow gum oozes out, quickly solidifies, and is collected and purified. This gum resin has been used medicinally for a long time in Ayurveda, spanning several hundred years. It was first mentioned in the *Atharva veda*, then in the first texts of Ayurveda, the *Caraka Samhita*, and *Sushruta Samhita*, and later in numerous other texts, for its effectiveness on the heart, obesity, and diabetes.⁴ Scientific investigation on *Commiphora wightii* has centered mainly on the anti-inflammatory effect and its hypolipidemic effect, for which it is an official drug in the *Indian Herbal Pharmacopoeia*, 2002.⁵

In *Sushruta Samhita*, there is a description of the changes that occur in cases of obesity, which remarkably parallels the modern interpretation of the etiology and pathogenesis of atherosclerosis.^{6,7} The *Sushruta Samhita* also deals with the treatment of obesity and of lipid disorders, and the consequences associated with the various conditions. However, the age of the resin is considered to play an important role in the kind of effect produced—an old sample being useful in reducing body weight and lipid levels, whereas a new sample of the gum can have the reverse effect.⁷ The crude gum also needs to be purified, as described in ancient texts, by boiling in a decoction of *triphala* (equal quantities of *Terminalia chebula*, *Terminalia belerica*, and *Emblica officinalis*) in order to free it from side effects such as skin rashes, diarrhea, irregular menstruation, restlessness, and hiccup.⁷

The gum resin has a complex composition with approximately 0.4 percent of an essential oil containing myrecene, dimyrecene, several steroids, Z- and E-guggulsterones, considered important for the hypolipidemic properties, and guggulsterols I-VI. Sesamin and cholesterol are found as well.^{4,5}

The cholesterol-lowering properties of the crude gum resin and various fractions have been studied extensively over the years. The first report in 1966 showed that the crude gum could protect cholesterol-fed rabbits against atherosclerosis and also significantly reduce serum cholesterol levels in hypercholesterolemic rabbits,⁸ apart from a reduction in the body weight of the treated animals.⁹ The

hypcholesterolemic effect has been shown by other workers in several species of experimental animals.^{7,10} The activity has been found to be in the steroid fraction, especially in the two ketonic steroids Z- and E-guggulsterones.¹¹ The two guggulsterones have also been shown to inhibit platelet aggregation.¹²

Several theories have been propounded to explain the hypolipidemic activity of the gum resin. Guggulsterone exhibits potent antioxidant activity¹³ and reversed myocardial necrosis induced by isoproterenol in rats.¹⁴ The gum resin^{15,16} and Z- guggulsterone¹⁷ have been shown to stimulate the thyroid, and the gum has also been shown to induce triiodothyronine production.¹⁸ In addition, Z-guggulsterone acts as an Bile Acid Receptor (BAR) antagonist¹⁹ and also as an antagonist of farnesoid X receptor FXR;²⁰ this may contribute to the cholesterol-lowering activity of the guggulsterones and of the gum resin.

Several trials have been conducted on the gum resin of *Commiphora mukul*, the so-called fraction A, and on guggulipid, which is the standardized ethyl acetate fraction of *Commiphora mukul* containing 2.5 percent guggulsterones developed at the Central Drug Research Institute, Lucknow, India.

Gum guggul

In preliminary open clinical trials, *guggul* was given in doses of 12-16 g per day to 22 patients with hypercholesterolemia associated with disorders such as obesity, ischemic heart disease, hypertension, etc. for a period of 12 weeks. At the end of the treatment period, it was observed that there was a fall in cholesterol levels by 33 percent in 96 percent of the cases, fall in triglycerides by 32.7 percent in 88 percent cases, decrease in free fatty acids by 62 percent, and decrease in serum phospholipids by 40 percent. In addition, there was a decrease in the body weight of ten patients by 1.4 kg every month.⁸

Gum *guggul* was also tried on 12 patients with elevated lipid levels—9 patients were obese, 2 had ischemic heart disease, and 1 patient had cerebral thrombosis. Treatment with *guggul* lowered the serum turbidity and prolonged the coagulation time.²¹

Other trials with gum *guggul* were held on patients with obesity/hyperlipidemia at several centers and confirmed the significant

lowering of not only the serum cholesterol level, triglycerides, and total lipids but also of nonesterified fatty acids.²²⁻²⁵ Two of these trials also compared the efficacy of Fraction A with gum *guggul*.^{22,23} A significant increase in HDL cholesterol has also been reported apart from lowering of other lipid parameters.²⁶

Fraction A

Petroleum ether extraction of *guggul* led to three fractions named A, B, and C, of which fraction A was found to have the maximum lipid-lowering action in chicks²⁷ and therefore was subjected to clinical trials. In a clinical study with 44 patients, fraction A was compared with clofibrate and an experimental drug from Ciba. In 20 patients 0.5 g fraction A was given twice a day for periods varying from 6 to 34 weeks. In the trial, patients were randomly assigned to receive one of the drugs. On analysis, fraction A was found to lower the serum levels of total lipids, triglycerides, cholesterol, phospholipids, and beta lipoprotein. In addition, the lowering of triglycerides was best in fraction A of *guggul*. Side effects observed with fraction A were hiccups (1 patient), diarrhea (3 patients), and restlessness and apprehension (1 patient).²⁸

In a long-term study, 41 cases of hyperlipoproteinemia were treated with 0.5 g of fraction A thrice daily for 75 weeks with 10 cases on 2 g·day⁻¹ of clofibrate also for 75 weeks serving as a comparative control. The reduction seen with fraction A was statistically significant for the entire treatment period. The reduction of cholesterol was 26.2 percent with *guggul* as against 31.5 percent with clofibrate, whereas for triglycerides the reduction for *guggul* was 36.5 percent as against 33.3 percent for clofibrate. Side effects such as diarrhea were seen in five patients.²⁹

This was also borne out in a clinical study on 40 obese, 40 hypercholesterolemic, and 40 hyperlipemic patients. The effect of gum *guggul* 2 g thrice daily or fraction 'A' 0.5 g twice daily was studied. Fraction A was able to significantly reduce the serum cholesterol and serum lipids in 21 days, in a manner similar to clofibrate.²³

In another double-blind cross-over study with fraction A, again with a dose of 1.5 g·day⁻¹ for 4 weeks at a time, in 48 hypercholesterolemic patients with a mean level of 280 mg percent of cholesterol brought

about a significant reduction of total cholesterol, total lipids, and triglycerides.³⁰

Studies on human beings and on experimental animals to elucidate the mechanism of action of fraction A showed that there was mobilization of cholesterol from the tissues, a decrease in its synthesis, and increased excretion of cholesterol leading to a fall in cholesterol levels.³¹

Guggulipid

Guggulipid is the standardized ethyl acetate extract of gum *guggul*. It has been suggested that the hypolipidemic effect of guggulipid is dependent upon the etiology of the disease with nondiabetic hyperlipidemic patients being benefited with significant lowering of cholesterol, triglycerides, total lipids, and beta lipoprotein, whereas no such effect was seen in diabetic patients.³²

In a phase I safety study, 400 mg guggulipid administered thrice a day for 4 weeks to 21 patients of primary hyperlipidemia was shown to be without any adverse effect on liver function, blood sugar, blood urea, hematological parameters, and ECG. There was also a significant lowering of cholesterol and/or triglycerides in 15 patients at the end of 4 weeks.³³

In a comparative cross-over trial, guggulipid (500 mg every 8 hours) was evaluated against clofibrate (500 mg every 8 hours) in 30 patients of primary hyperlipidemia and judged to have better hypolipidemic activity than clofibrate.³⁴ A dosage of 500 mg of guggulipid was given thrice a day for 6 weeks to evaluate its usefulness in 22 patients of primary hyperlipidemia. The serum cholesterol levels were significantly lowered in 59 percent of patients, the effect beginning to be seen after 2 weeks and reaching a maximum in 4-6 weeks. The fall in cholesterol levels and triglycerides was 24.5 and 27 percent, respectively. There was a return to pretreatment values within 6 weeks of stopping the drug. The drug was well tolerated.³⁵

In 25 patients with nephrotic syndrome, 75 mg three times a day of guggulipid was given for 12 weeks. HDL cholesterol levels increased after 8 weeks, although significant changes in the electrocardiogram were seen only after 12 weeks of therapy.³⁶

In a randomized double-blind trial in 61 patients with hypercholesterolemia, 31 on guggulipid and 30 on placebo, patients were given 50 mg of guggulipid or placebo capsules for 24 weeks along with a diet rich in fruits and vegetables. Guggulipid decreased the total cholesterol, LDL cholesterol, triglycerides, and total cholesterol/high-density lipoprotein cholesterol ratio by approximately 11-12 percent with no changes being observed in the placebo group. Lipid peroxides also decreased by about 33 percent in the guggulipid group, whereas the placebo group remained unchanged. The HDL cholesterol level was unchanged in both groups. After a wash-out period of another 12 weeks, changes in lipoproteins were again reversed in the guggulipid group, with no changes being observed in the placebo group. The overall impression was that the combined effect of diet and guggulipid was equal to that of modern drugs.³⁷

In another randomized-controlled trial³⁸ guggulipid was given in two dose levels three times a day of 1,000 mg and 2,000 mg or matching placebo in 103 cases of hyperlipidemia for 8 weeks. It was found that there was an increase in LDL cholesterol in both 1,000 mg as well as 2,000 mg dosage groups when compared to placebo where there was a decrease. It appears that there was no favorable effect on lipid levels. The dose given is much above the dosage for guggulipid, although standard doses were also tried out. In addition, six patients on guggulipid showed skin rashes reduced by prior processing of the gum to remove impurities.⁹ Skin rashes are also encountered when larger doses are used. The age of the resin is considered to play an important role on lipid-lowering activity levels and needs to be taken into consideration.⁷

Coronary artery disease

In an exploratory trial, gum *guggul* fraction A was given at a dose of 500 mg twice a day to both healthy subjects and coronary artery patients. In healthy subjects, it produced a 22-percent increase in serum fibrinolytic activity within 24 hours of administration, whereas it increased to 40 percent after 30 days. In coronary artery patients, it was found that the serum fibrinolytic activity increased by 19 percent after 24 hours and reached 33 percent after 30 days. A reduction in

the platelet adhesive index by 19 and 16 percent in healthy controls and in patients, respectively, was also seen.³⁹

In another study, of the 42 patients with coronary artery disease, only 21 patients were given 1.5 g of *Commiphora mukul* every day, whereas the remaining patients were not. It was found that patients receiving the drug showed reduction of euglobin lysis time and increase in fibrinolytic activity, whereas controls did not show any change in these parameters. There was no significant change in platelet aggregation.⁴⁰

Ischemic heart disease

In a trial, 135 patients with ischemic heart disease and symptoms of precordial pain, dyspnea on effort, history of angina, or previous history of myocardial infarction were included. Of these, 110 patients served as the treatment group, and 25 patients were kept as the control group. The clinical profile and changes in serum lipids were evaluated at monthly intervals for the various parameters, whereas ECG was evaluated before and after treatment. Purified *guggul* powder was given in a dose of $8 \text{ g} \cdot \text{day}^{-1}$ for 3 months. There was a fall in lipid parameters comparable to clofibrate. Precordial pain and dyspnea also improved and grades I and II patients became absolutely free of the symptoms. Patients of grade III and IV also showed improvement. There was a reduction in weight of an average of $1 \text{ kg} \cdot \text{month}^{-1}$. ECG changes were seen in seven cases with improvement in S-T segment depression and inversion of T-wave in patients of long-standing ischemia.⁴¹

Side effects associated with *guggul* are generally gastrointestinal in nature, reduced by purification of the resin and seen more often with larger dosages.⁴ These include diarrhea, skin rashes, headache, irregular menstruation, and restlessness.⁷ It has been shown not to have acute, subacute, and chronic toxicity in rats, dogs, and monkeys. Since it increases menstrual discharge it is not to be taken during pregnancy.⁵ *Guggul* inhibits platelet aggregation,¹² and is probably best avoided with other blood thinning agents. *Guggulipid* given at a dose level of 400 mg thrice a day for 4 weeks showed no adverse effect on liver function, blood sugar, blood urea, and hematological parameters.³³

Considering the variable nature of the preparation used in the different trials, it would be useful to conduct trials with well-defined material, along with dosage studies. It would be important to take into account the age of the resin, since old resin is said to have a beneficial effect on obesity as mentioned in the *Sushruta Samhita*.^{7,42} Thus, it would be necessary to identify components that may be responsible for having a reverse effect of increasing lipid levels.

***Trigonella foenum-graecum* Linn. (Family: Fabaceae)**

Sanskrit: Methika	Tamil: Vendium
Hindi: Methi	English: Fenugreek

See Chapter 11 for an introduction to fenugreek. Fenugreek seeds have been shown to reduce lipid levels in a number of experimental animals such as rats, dogs, and rabbits.⁴³⁻⁵⁰ There was significant reduction of serum cholesterol levels ($p < 0.00005$) in both normal (42 percent) and hypercholesterolemic (58 percent) rats on feeding with a diet of 50 percent *Trigonella foenum-graecum* seeds.⁴³ The saponin fraction that interacts with the bile salts has been shown to reduce cholesterol levels in rats.^{45,46} In rats the ethanol extract contains hypocholesterolemic constituents like saponins, which led to a 18-26 percent reduction in plasma cholesterol.⁴⁶ In dogs the lipid extract had no effect on cholesterol levels, but the fiber-rich (53.9 percent) and saponin-containing (4.8 percent) defatted portion showed significant reduction of cholesterol levels in normal and in hypercholesterolemic dogs.⁴⁸ A principle isolated from the aqueous extract showed hypoglycemic, hypocholesterolemic, and hypotriacylglycerolemic activities in hyperlipidemic rabbits.⁴⁹ Different levels of fenugreek and extracts were tried on rabbits both in normal animals and those pretreated with a high fat diet. Plasma cholesterol levels were reduced in both groups; however, reduction in triglyceride levels was seen only in the high fat diet group when animals were treated with 30 percent of diet enriched with seed powder or extracts; changes in cholesterol, triglycerides, and LDL cholesterol were seen. There was

no change in HDL cholesterol but the ratio of HDL to LDL changes favorably.⁵⁰

Clinical studies have demonstrated the beneficial effect of fenugreek seeds in hyperlipidemic patients and in diabetic patients. For trials on diabetic patients see Chapter 11, "Antidiabetic agents."

In an open exploratory trial 10 hyperlipidemic patients were given isocaloric diets with or without the addition of 100 g of debitterized fenugreek powder for 20 days. Patients receiving a diet with added fenugreek showed significant reduction in total serum cholesterol, LDL, VDL cholesterol, and triglyceride levels. HDL cholesterol did not change but ratios with respect to total cholesterol and LDL and VLDL showed a favorable change.⁵¹

In patients with mild to moderate hypercholesterolemia,⁵² fenugreek seeds were able to reduce cholesterol levels. In another open trial, 20 hypercholesterolemic patients, ages 50-65 years, were given germinated fenugreek seeds powder in packets of 12.5 g and 18 g to incorporate daily one packet into any food of their choice for 1 month. It was found that fasting blood levels taken one day before the start of the trial and after the treatment period of 1 month showed significant reduction of total cholesterol and LDL levels at the 18 g dose level, although there was a hypolipidemic effect at both levels. No significant change in HDL, VLDL, and triglyceride levels was seen in any of the patients. Germination was found to bring about definite changes in the soluble fiber content of the seeds.⁵³

In a single blind trial with placebo control, 18 hypercholesterolemic patients were divided into three groups and were given 50 g packets of defatted deodorized fenugreek seed powder (FG), 50 g placebo powder, or 25 g placebo powder plus 25 g FG powder to be taken orally before lunch and dinner for 20 days. Lipid profiles were checked with fasting blood samples on 0, 10, and 20 days. Significant changes in total cholesterol, triglycerides, and VLDL levels were seen in both the fenugreek groups as compared to placebo.⁵⁴

The safety of fenugreek is covered in Chapter 11 "Antidiabetic agents."

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OTHER HYPOLIPIDEMIC PLANTS

***Emblica officinalis* Gaertn. (Family: Euphorbiaceae)**

The use of the fruits of *Emblica officinalis* (see Plate 1 in color gallery) in the treatment of acidity, gastritis, dyspepsia, and acid peptic ulcer has already been dealt with in Chapter 3, "Gastrointestinal agents." Experiments on small animals, notably rabbits, have shown that fruits of *Emblica* have a beneficial effect on cholesterol levels in atherosclerosis¹⁻³ in the serum, aorta, and liver.⁴ Rabbits that were made hypercholesterolemic by cholesterol feeding and a fat-rich diet were then fed 5 ml·kg⁻¹ body weight of fresh *Emblica officinalis* juice per day for 60 days. Serum cholesterol fell by 82 percent, triglycerides by 66 percent, phospholipids by 77 percent, and LDL levels by 90 percent. In addition, tissue lipid levels and aortic plaques showed reduction.⁵ Flavonoids from *Emblica* have been shown to exert a very potent hypolipidemic and hypoglycemic effect in rats⁶ by reducing synthesis and increasing the degradation of cholesterol.⁷

In an open study, supplementation of the diet of normal and hypercholesterolemic men aged 35-55 years with *Emblica officinalis* for 28 days showed that both groups of subjects showed a decrease in cholesterol levels, which rose to initial values 2 weeks after the withdrawal of supplementation.⁸ Further studies need to be carried out.

See Chapter 3, "Gastrointestinal agents" for safety of *Emblica officinalis*.

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ANTIHYPERTENSIVE PLANTS

Plants are not the first line of treatment for hypertension; however, the use of *Rauwolfia serpentina* led to the isolation of reserpine as an antihypertensive, which has now fallen into disuse because of the side effects of the molecule. Nonetheless, the search for possible herbs for treatment of hypertension continues.

***Coleus forskohlii* Briq. (Family: *Lamiaceae*)**

Latin: <i>Coleus barbatus</i> Benth.	Hindi: Gurmāl
Sanskrit: Makāndi, Mayini	English: Kaffir Potato

Coleus forskohlii is a perennial herb, which is found throughout India in the plains and in the subtropical Himalayan region. Other species of *Coleus* are used in Ayurveda,¹ and there is a divided opinion on this species being mentioned in the traditional texts. The

drug with the Sanskrit name *Makandi* is mentioned in various texts starting from about 1340 AD with the *Raj Nighantu* and it being equated with *Coleus forskohlii*.² It is used by tribals externally for skin problems, boils, eczema, cough, and as a tonic. The plant has tuberous roots that are used as a vegetable and also used medicinally. A labdane diterpene, coleonol, better known as forskolin, was isolated from the roots and shown to have antihypertensive and positive inotropic effect. Forskolin has been shown to have significant hypotensive activity in anesthetized cats and rats and also in hypertensive rats because of the relaxation of vascular smooth muscle.^{3,4,5}

In an exploratory trial, 14 patients with hypertension were treated with 100-200 mg of *Coleus forskohlii* root powder taken thrice a day. Out of 14 patients, 13 responded to the treatment within 4-15 days.⁶ Another pilot study revealed that using ethanolic extract of *Coleus forskohlii* in 23 patients at a dose of 165 mg extract per capsule taken thrice a day for 3 weeks brought down both systolic and diastolic blood pressure. Therefore, the group was increased and 37 patients were divided into two groups: the first group of 28 patients received 1 capsule thrice a day and the other group of 9 patients with blood pressure levels of 190 mm systolic and 100 mm diastolic received 2 capsules thrice a day for 6 weeks. The blood pressure fell continuously for 5 weeks after which no further fall was seen. There was also decrease in serum cholesterol, creatinine, and in blood urea. It was estimated that most patients required $15 \text{ mg} \cdot \text{day}^{-1}$ of coleonol (forskolin) to be present in the extract, although patients with higher blood pressure required $30 \text{ mg} \cdot \text{day}^{-1}$. The drug was well tolerated and no major side effects were observed.⁷ The results obtained warrant further studies with controls and larger patient numbers.

Coleus forskohlii roots are eaten in North India for the treatment of cough.¹ In the clinical trial using standardized extract of roots no major side effects were seen.⁷

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VENOUS DISORDERS

There are two kinds of veins that help return blood to the heart—the superficial veins, which constitute 10 percent, and deep-seated veins, which constitute 90 percent. The superficial veins have valves that if not working can lead to stagnation of blood, pain in the legs, twisted contorted veins, and edema. Inadequate return of blood is termed venous insufficiency, which can lead to varicosity of veins or varicose veins. This can stem from lack of movement either because of the sedentary nature of work involving sitting at the desk or from professions involving long hours of standing.¹

***Centella asiatica* (Linn.) Urban. (Family: Apiaceae)**

Latin: *Hydrocotyle asiatica* Linn.

Tamil: Vallarai

Sanskrit: Mandukaparni

English: Indian Pennywort

Hindi: Brahma Manduki

Centella asiatica (see Plate 8 in color gallery) is a slender, creeping herb found in moist areas. The plant and the leaves are used medicinally for a variety of conditions. However, *Centella asiatica* is

best known in India as a mental rejuvenator (*medhya rasayana*) or memory tonic for reducing mental fatigue and improving mental clarity. For details see Chapter 12, “Central nervous system agents.” It has also been used extensively for improving skin conditions of varied etiology and for healing of wounds and ulcers, both internally and externally. See Chapter 9 for its effect on wound healing. It is traditionally used for improving blood circulation and reduction of edema stemming from debility.^{2,3}

The major chemical constituents are the triterpenoid saponins—madecassoside and asiaticoside—and their aglycones—asiatic acid and madecassic acid. Several other saponins including brahmoside and brahminoside, triterpenoid acids, and an alkaloid hydrocotyline have been isolated.⁴

Scientific studies based on clinical and pharmacological data have shown that it is useful in venous hypertension, venous insufficiency, and in varicose veins since it is useful in lowering levels of lysosomal enzymes that are considered responsible for valvular damage.⁵ The triterpene glycoside, asiaticoside, has been shown to hasten wound healing by increasing collagen I synthesis.⁶ Most of the trials have been conducted with the total triterpene fraction (TTFCA) or the titrated extract of *Centella asiatica* (TECA) containing 30 percent asiatic acid, 30 percent madecassic acid, and 40 percent asiaticoside; however, a lipid preparation with *Centella asiatica* as major component has been recommended for capillary fragility.⁷

Extracts of *Centella asiatica* showed a positive effect on mucopolysaccharide metabolism when tried on patients with varicose veins. Basal levels of uronic acids and lysosomal enzymes are elevated in varicose vein patients, which indicate an increased mucopolysaccharide turnover in these patients. Treatment with 60 mg·day⁻¹ for 3 months of the active triterpenic fraction led to lowering of elevated values of uronic acid and lysosomal enzymes resulting in improved vein tonicity, vein dispensability, and decrease in subjective complaints in 80 percent patients with venous insufficiency of the lower limbs.⁸

In a single-blind placebo-controlled trial, 89 patients with venous hypertension microangiopathy were treated with *Centella asiatica* extract. It was found that there was significant difference from the placebo

of all the parameters tested,⁹ so that it was possible to distinguish between 60 and 120 mg daily.¹⁰ Several models have been used to test the effect of *Centella asiatica* extract at two different dosage levels against placebo in venous hypertension and are reported in the October 2001 issue of *Angiology*.¹¹ Symptoms of venous hypertension such as ankle edema, pain and cramps, tiredness, and restless lower extremities improved in the treated groups on 30 and 60 mg of *Centella asiatica* extract (TTFCA) thrice a day.¹²

In another study, 10 normal subjects, 22 with moderate superficial venous hypertension, and 12 with postphlebitic limbs and severe hypertension were studied first for 2 weeks without treatment and then after administering 60 mg *Centella asiatica* extract three times a day for 2 weeks. There was also improvement in capillary permeability in patients both with moderate superficial venous hypertension and severe venous hypertension having ankle and foot edema in the evening.¹³

In a double-blind placebo-controlled trial, 94 patients with chronic venous insufficiency were administered either 60 or 120 mg per day of *Centella asiatica* extract (TECA) for 8 weeks. There was improvement in the feeling of heaviness in the limbs, edema, and in vein dispensability in the treated group, although vein dispensability increased in the placebo group.¹⁴

The trials have been conducted using special extract or combinations of isolated components. It would be useful to study the effect of standardized plant material or simpler whole extracts to extend the scope of usage.

Centella asiatica is generally considered safe and has a low degree of toxicity. It is traditionally considered a vegetable and consumed as food. No adverse reactions have been reported in doses commonly used. No mortality has been reported in mice up to 5 g·kg⁻¹ body weight.¹⁵

NOTES

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Chapter 7

Urinary Tract Drugs

In Ayurveda, plants have been used to maintain the proper functioning of the kidneys and the urinary tract. The various disease conditions of the kidneys and the urinary tract described in Ayurveda have their closest equivalents in modern parlance to urinary tract infections (*mutra kricchra*), urinary stones (*asmari*) and obstructive uropathies (*mutragatha*).

DIURETICS

Diuretics remove excess water from the body by increasing urinary excretion. This is useful in conditions like high blood pressure, heart failure, glaucoma, edema, nephrotic syndrome, and liver cirrhosis.¹ *Mutra virechanya dravya* is the Ayurvedic equivalent of diuretics.² Over 150 plants have been reported to be diuretics.³ Plants like *Boerhaavia diffusa* and *Tribulus terrestris* are rich in potassium. The herbal diuretics in Ayurveda are considered mild and nontoxic. However, only a few of them have been investigated to some degree and further long-term studies are required.

***Boerhaavia diffusa* Linn. (Family: Nyctaginaceae)**

Latin name: *Boerhaavia repens*
Linn.

Hindi: Biskhafra

Sanskrit: Punarnava

Tamil: Mukkarete

English: Spreading hogweed

Boerhaavia diffusa is a spreading plant with a thick perennial root found growing throughout India up to an altitude of 2,000 m. Both the whole plant and the root have been used in medicine for a variety of conditions; however, it is most widely used in Ayurveda for treating renal and urinary problems. The tender shoots are eaten as a vegetable. The plant has traditionally been used to reduce edema associated with kidney, heart, gastrointestinal tract disorders, and general debility. In addition, it is a cardiogenic, has laxative and diuretic activity, is useful in fever, and acts as a rejuvenative or *rasayana*. It has both diuretic and anti-inflammatory properties and therefore is useful in inflammatory renal diseases.⁴ The plant has an official status in the *Indian Herbal Pharmacopoeia*, 2002, as a diuretic and hepatoprotective agent.⁵ It has been used to treat edema and ascites resulting from early cirrhosis of the liver and in chronic peritonitis. See Chapter 4, "Hepatoprotective agents."

Boerhaavia diffusa contains an antifibrinolytic glycoside—punarnavoside, alkaloids, rotenoids (boeravinones A, B, C, D, E), lignans (liridoderdin, syringaresinol mono β -D-glucoside), flavones, ursolic acid, sterols (β -sitosterol), boeravine, β -ecdysone, hypoxanthine 9-L-arabinofuranoside, and potassium salts.^{4,5}

Pharmacological studies have shown that the plant has both diuretic⁶ and anti-inflammatory activities^{6,7} with maximum activity being seen in samples collected during the rainy season.⁴ When the various parts of the plant were tested, it was found that the extracts of leaves and roots showed significantly more anti-inflammatory and diuretic activities as compared to the whole plant.⁸ In addition, the alkaloidal fraction has been shown to have immunomodulatory activity.⁹ *Punarnava* has also been found useful in acute pyelonephritis in albino rats,¹⁰ and has been found to exhibit a diuretic effect equivalent to furosemide.¹¹

The initial trials were more exploratory in nature with very few patients, inadequate inclusion criteria, and lack of objective end points, which, however, served to give a clinical impression of the nature of the drug. The first trial included 5 cases of parenchymatous nephritis along with 19 cases of dropsy and jaundice, which were treated with *Boerhaavia diffusa*. It was found that the increase in urine output was accompanied by a decrease in the albumin content, and a decrease in

specific gravity of the urine.¹² Clinical trials to evaluate the diuretic effect of *Boerhaavia diffusa* were also conducted in 34 patients suffering from edema and dropsy because of varied causes using liquid extracts derived from both the dry and fresh plant and found that they were equally effective in the reduction of edema.¹³

A total of 22 patients diagnosed with nephrotic syndrome were randomly allocated to one of two groups and treated with either *punarnava* crude drug—as powder or in the form of decoction—or steroids and diuretics in the control group. There were several drop-outs and only 15 patients completed the trial—12 in the drug group and 3 in the control group. Of the 12 patients who completed the trial 4 patients were relieved and 7 improved, whereas 1 patient showed deterioration. In the control group, two patients were relieved, whereas one improved. It was observed that the treatment with *punarnava* induced a slow and prolonged diuresis, and patients had relief in edema and a decrease in albuminuria with increase in protein levels.¹⁴

In an open trial, 40 patients with nephrotic syndrome presenting edema, burning micturition, and albumin in urea were treated with three 500 mg capsules of fresh powder of *Boerhaavia diffusa* given thrice a day for 1 month. It was found that there was an increase in serum protein level and a reduction in urinary protein excretion in patients. Of the 27 patients who were severely anemic before the start of the trial 6 came into the normal range. There was a moderate decrease in blood urea and a significant reduction in serum creatinine concentration, whereas serum protein levels showed an increase. Levels of serum sodium and potassium showed only marginal changes and the final level depended on the initial values, the diet, and the primary condition of the patients. The level of immunoglobulins also tended to become normal.¹¹

The aerial parts of *Boerhaavia diffusa* are eaten as a vegetable and the plant is well tolerated, although it may show a laxative effect in some patients.¹⁵ The drug may cause vomiting in larger doses because of its emetic properties.^{5,16} The acute oral toxicity of a lyophilized decoction and juice of fresh leaves showed no toxicity in mice up to 5 g·kg⁻¹.¹⁷ The alcoholic extract of whole plant did not show any

toxicity in mice up to an oral dose of $2 \text{ g} \cdot \text{kg}^{-1}$.¹⁸ No teratogenic effect was seen in experimental animals.¹⁹

Further trials are needed with standardized drug, dosage studies, objective parameters, and larger patient numbers since the early studies have served to give an impression of the clinical utility of the drug.

***Tribulus terrestris* Linn. (Family: Zygophyllaceae)**

Sanskrit: Gokshura	Tamil: Nerunji
Hindi: Gokhru	English: Puncture Vine, Land Calotrops

Tribulus terrestris is an annual herb found growing throughout India up to an altitude of 5,400 m. The plant has bright yellow flowers appearing after the rains, followed shortly by prickly fruits, which are medicinally important. The fruits are best known in Ayurveda for their diuretic action, and are thus considered helpful in burning micturition, chronic cystitis, and in expelling renal and urinary calculi.²⁰ The fruits are also used as an aphrodisiac for promoting strength and in heart problems.²¹ The dried ripe fruits have the official status in the *Indian Herbal Pharmacopoeia*, 2002, as a diuretic and an antiurolithiatic agent.²²

The fruits contain several steroidal saponins such as terrestrosins A, B, C, D, E; alkaloids; sterols such as β -sitosterol, campesterol, stigmasterol; flavonoids; cinnamic acid derivative (terrestiamide); tannins; and fixed oil. The saponins in the leaves and roots have a high hemolytic index, but are absent in the stems and seeds.^{20,22}

Studies conducted in several experimental animals have shown diuretic activity.²³⁻²⁵

In an open trial, 75 patients with mild to moderate hypertension (140-179 mm Hg systolic and 90-109 mm Hg diastolic) were divided into three groups of 25 each. Two groups of 25 each, apparently under same conditions, were treated with $3 \text{ g} \cdot \text{kg}^{-1}$ in three divided doses of aqueous extract of *Tribulus terrestris*. Group A received the whole-plant extract, group B the fruit extract, whereas the control group of 25 patients was given a similar dose of lactose for 4 weeks.

Patients were assessed at the end of every week both for the presenting symptoms of headache, giddiness, insomnia, etc. and objective parameters such as systolic and diastolic blood pressure, and also urinary volume, pulse rate, and serum cholesterol. Both drug-treated groups showed a significant fall in both diastolic and systolic blood pressure, whereas there was no significant change in the placebo group. There was maximum improvement in headache and giddiness in group A (whole-plant extract), whereas group B (fruit extract) showed improvement in palpitation and swelling.²⁶

It has been reported that the drug causes toxicity in sheep in Australia and in South Africa. It has been suggested that this is due to the presence of the alkaloids harmaline and norharmaline that accumulate in the body, as a result of which the animals stagger.²⁷ In an experiment in India in which 4 lb of fresh *Tribulus terrestris* was given to goats and sheep and 8 lbs to calves, no toxic effect was observed during the observation period of 1 month. Similarly during daily feeding of 1 kg plant juice for 8 days to calves and sheep, no toxicity was seen.²⁸ Some toxicity has also been reported in mice. However, it is considered a safe drug in man.²⁹ No side effects were reported in the trial for use as an antihypertensive.²⁶ In a clinical trial conducted on 406 patients using the saponin of *Tribulus terrestris* over a long period, no toxic effects were seen on blood picture, liver, and kidney.³⁰

NOTES

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PLANTS FOR URINARY TRACT DISORDERS

***Crataeva nurvala* Buch.-Ham (Family: Capparidaceae)**

Latin: *Crataeva* = *Crateva*. *Crataeva magna* (Lour) DC, *C. religiosa* var. *nurvala* (Buch.-Ham.) Hook.f. & Thom.

Sanskrit: Varuna

Hindi: Varun

Tamil: Maralingam

Crataeva nurvala (see Plate 9 in color gallery) is a deciduous tree found throughout India, well known for its handsome foliage and beautiful cream-colored flowers. The ash-gray stem bark is used in Ayurveda for treating urinary disorders both as a single drug and also in combination with other drugs. Thus, it has been used for the treatment of urinary stones, for benign prostatic hypertrophy (BPH), and for treating urinary infections. It is also used to improve appetite and is used both internally and externally to treat rheumatism. However, it is best known for its action on urinary calculi and it has an official status in the *Indian Herbal Pharmacopoeia*, 2002, as an anti-urolithiatic drug.¹

The major constituent is the triterpene lupeol (0.6 percent), which has been shown to have antilithotriptic activity. Other constituents are the alkaloids (cadabicine, cadabicine diacetate, and cadabicine dimethyl ether), minor flavonoids [(-)-catechin, (-)-epicatechin 5-glucoside, and (-)-epiafzelechin], sterols (diosgenin, β -sitosterol, β -sitosterol acetate,

lupeol acetate, α -spinosterol acetate, α -taraxasterol, 3-epilupeol, lupe-none), triterpenes (betulinic acid, friedelin, varunol), flavonoids (rutin, quercetin), and the isothiocyanate glucoside—glucocapparin.^{1,2}

Benign prostatic enlargement

The equivalent of benign prostatic enlargement or enlargement of the prostate gland leading to difficulty in passing urine is known as *mutragranthi* in Ayurveda (*mutra*: urine; *granthi*: knot or block). *Crataeva nurvala* is considered useful in *mutragatha* or various obstructive conditions of the urinary tract.²

The bladder function of ten dogs was studied using flow cystometry after treatment with *Crataeva nurvala* for 40 days, which showed a hypertonic effect against the initial values.³ The ethanolic extract of *Crataeva nurvala* has shown anti-inflammatory activity in carrageenin-induced edema in experimental animals.⁴ The petroleum ether extract of the stem bark has shown anti-inflammatory activity in acute, subacute, and chronic models of inflammation.⁵ In addition, lupeol was shown to exhibit anti-inflammatory effect.^{6, 7}

In an open study on 30 patients with prostatic hypertrophy and resultant hypotonic bladder, 50 ml stem-bark decoction (prepared by boiling 1 part stem bark with 16 parts water, reducing to one-fourth and filtering) was given twice a day to patients and the bladder function examined using cystometric studies. It was found that patients experienced improvement in bladder tone with consequent relief in symptoms such as frequency of urination, incontinence, pain, and retention of urine. The force in expulsion of urine was also found to increase. In patients exhibiting hypotonia and atonia after prostatectomy, the decoction was found to increase bladder tone, whereas improvements were also seen in neurogenic bladder. The residual volume of urine decreases significantly.³

In an open study with 56 patients with enlarged prostate, 50 were on drug while 6 patients and 10 healthy subjects served as control. A total of 50 patients were treated daily with freshly prepared decoction of *Crataeva nurvala* stem bark as described above, dose in Indian measures of 4-6 tolas twice a day (5 tolas = 2 fluid ozs.) for a period of 6 months. Major presenting symptoms were retention of urine, dribbling, frequent micturition and burning, and difficulty in passing

urine. Most patients had mild renal insufficiency. The status of patients was evaluated after 3-4 weeks, 3 months, and 6 months of therapy. Seventy percent of patients had complete relief in symptoms at the end of 6 months, whereas the remaining patients had considerable relief. Initially 56 percent of patients showed hypotonia, 36 percent showed hypertonia, and a mere 8 percent were normotonic. However, at the end of 6 months, 75 percent of patients were normotonic with normal residual urine, whereas 25 percent were hypotonic with residual urine below 50 cc. The action of the drug was considered significant when compared to the small control group. This has been ascribed to the action on the bladder musculature and to its anti-inflammatory activity.⁴

Urinary stones

Stones in the urinary tract are termed *asmari* in Ayurveda (*asmam*: stone; *ari*: enemy; or enemy in the form of stone). There are different kinds of stones described in Ayurveda and comparison of the Ayurvedic descriptions with Western literature suggests that they correspond to differences in chemical composition.²

Decoction^{4, 8} of *Crataeva nurvala* and extract^{9,10} reduced significantly weight of stones in experimental animals. In calcium oxalate lithiasis, treatment with the decoction elevated levels of the oxalate-synthesizing liver enzyme glycolic oxidase and lowered the deposition of stone-forming constituents in the kidney. In addition, partial reversal of magnesium excretion prevented stone formation, since lower levels of magnesium tend to increase oxalate deposition.⁸ The pentacyclic triterpene lupeol has been shown to possess antiuro-lithiatic properties in albino rats at a dose level of 50 mg·kg⁻¹. Animals treated with lupeol showed reduced tendency to form stones, and very small stones were dissolved or flushed out.¹¹ Lupeol (25 mg·kg⁻¹ body weight) has been shown to reduce renal excretion of calcium oxalate and also to reduce renal tubular damage as seen by lowered levels of several urinary marker enzymes, which indicate renal tissue damage.¹² In addition, lupeol has antioxidant activity, which contributes to its protective action against calculosis.¹³

In an open trial, 46 patients with urinary stone were treated with 50 ml of stem-bark decoction of *Crataeva nurvala* administered twice a day for varying periods. It was found that 28 patients were spontaneously able to pass the stone in 1-47 weeks, whereas 18 patients had considerable relief in symptoms. The average time for passing the stones was 16 weeks for all except two patients who needed 36 and 47 weeks. The process of expulsion of the stone may be both due to the action of the drug in reducing the stone size and its action on the smooth muscle.³

A study of urinary electrolytes after 1 month of treatment with *C. nurvala* was found to alter the relative proportion of urinary electrolytes involved in calculus formation. Excretion of urinary calcium was greatly reduced, although that of sodium and magnesium was significantly increased. In addition, crystalurea was found reduced in 75 percent of patients.³

Another trial was carried out with 55 patients (calcium oxalate stones) in group A, 15 patients (calcium phosphate nephrolithiasis) in group B, and a control group (20 subjects). The decoction of the stem bark was given to patients for 12 weeks resulting in considerable reduction in pain (70.90 percent in group A; 73.33 percent in group B), and dysuria (63.63 percent in group A; 53.84 percent in group B), whereas some patients experienced radiological reduction in the size of stones (33.33 percent in group A; 35.72 percent in group B).¹⁴

Urinary infection

Urinary tract infection (UTI) is a very commonly found condition, and is generally of bacterial origin. Based on symptoms, UTI has been correlated with *mutrakrichhra vyadhi* in Ayurveda. Symptoms include discomfort associated with urination.¹⁵

In vitro studies showed that *Crataeva nurvala* extract showed antibacterial activity against strains causing urinary infections.¹⁶

In an open trial, *Crataeva nurvala* decoction was given to patients suffering from urinary tract infection for 4 weeks. There was relief in symptoms and absence of pus cells together with negative cultures in some patients; however, 68 percent continued to test positive for infection even while experiencing relief of symptoms.³

In a study, 84 patients with UTI were treated with stem-bark decoction of *Crataeva nurvala*. Of the 84 patients 55 percent had complete relief and 40 percent showed improvement.¹⁷

Thus *Crataeva nurvala* has several useful properties for urinary tract disorders combined together in one drug and deserves further studies to fully exploit its properties.

The decoction of stem and root bark are well tolerated.¹⁸

NOTES

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Emblica officinalis



PLATE 1. Illustration of *Emblica officinalis*.

Boswellia serrata



PLATE 2. Illustration of *Boswellia serrata*.

Andrographis paniculata

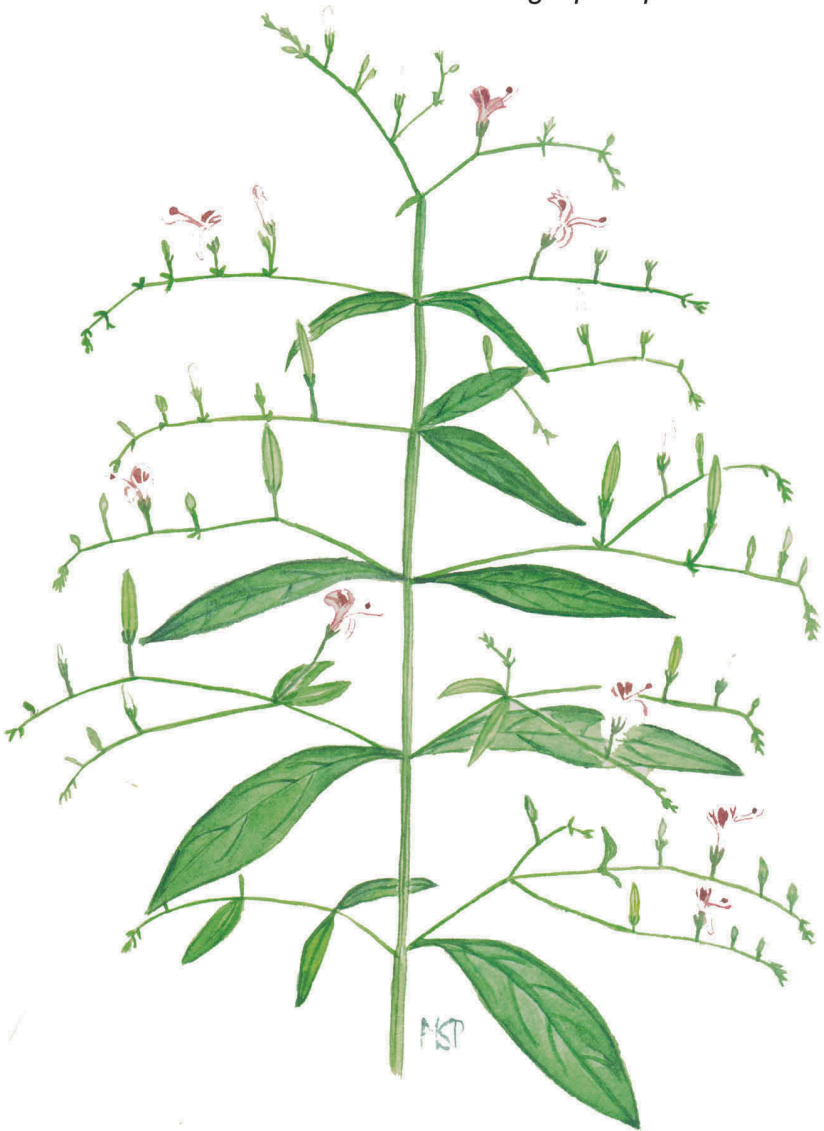


PLATE 3. Illustration of *Andrographis paniculata*.

Tinospora cordifolia

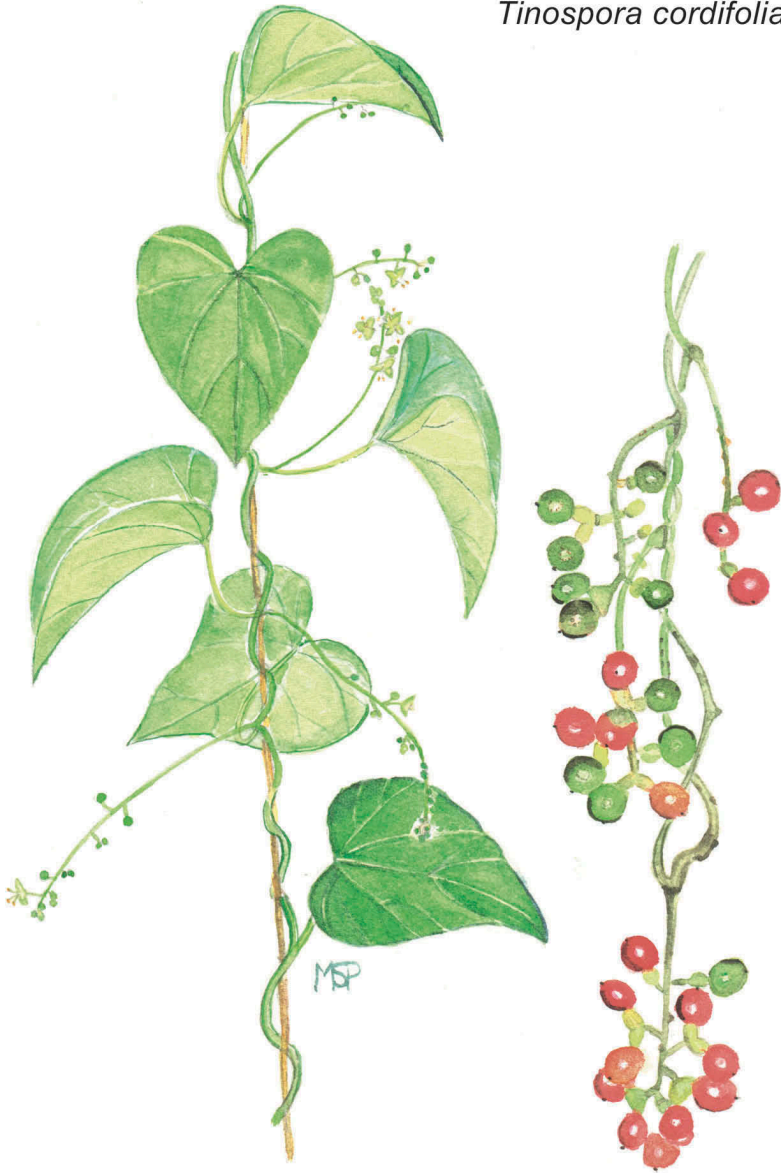


PLATE 4. Illustration of *Tinospora cordifolia*.

Phyllanthus amarus



PLATE 5. Illustration of *Phyllanthus amarus*.

Terminalia arjuna

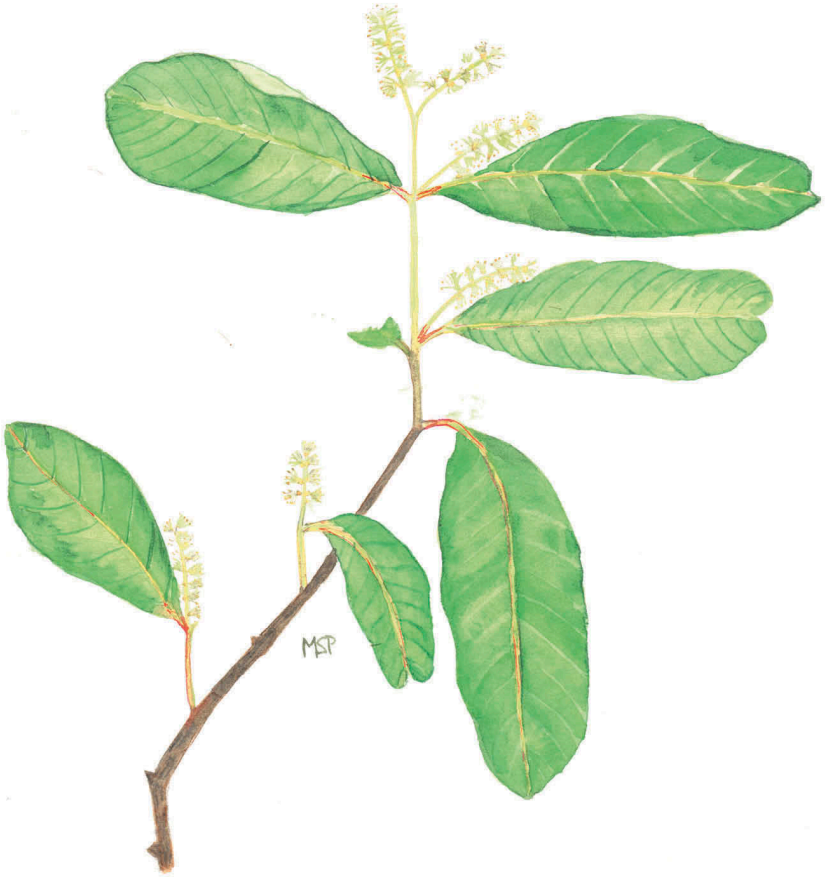


PLATE 6. Illustration of *Terminalia arjuna*.

Commiphora wightii



PLATE 7. Illustration of *Commiphora wightii*.

Centella asiatica

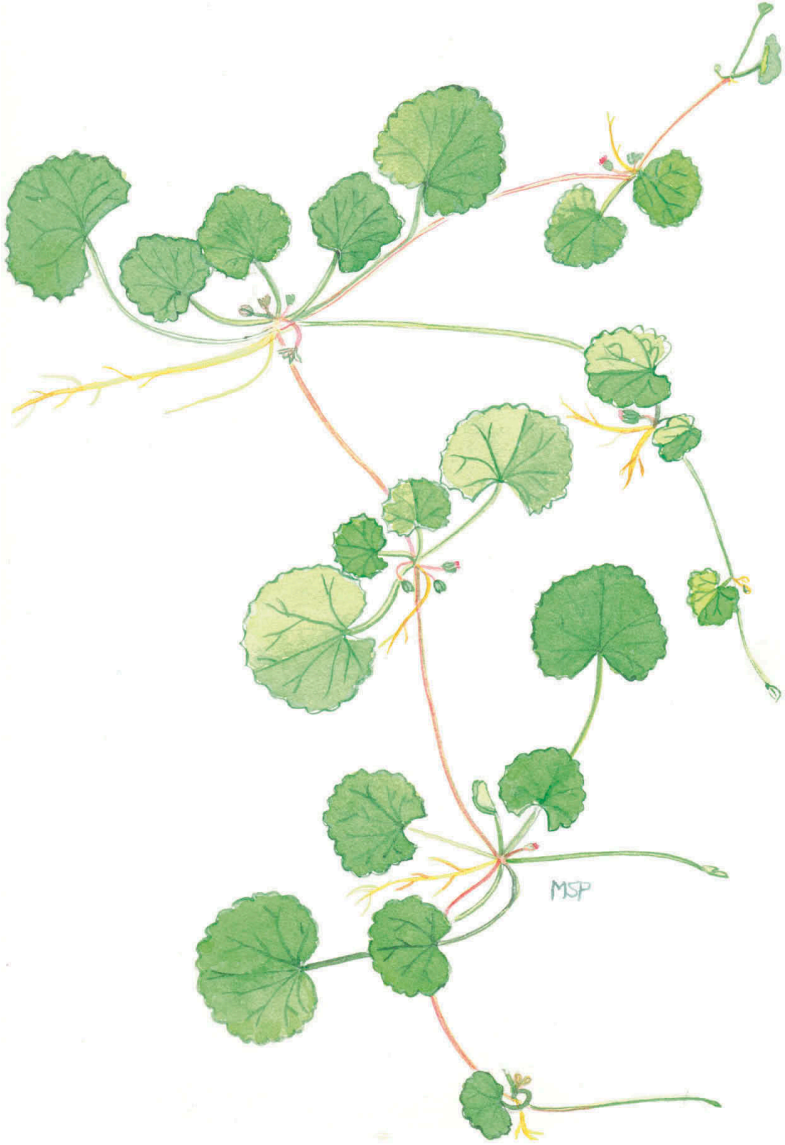


PLATE 8. Illustration of *Centella asiatica*.

Crataeva nurvala



PLATE 9. Illustration of *Crataeva nurvala*.



PLATE 10. Illustration of *Cissus quadrangularis*.

Gymnema sylvestre



PLATE 11. Illustration of *Gymnema sylvestre*.

Mucuna pruriens



PLATE 12. Illustration of *Mucuna pruriens*.

Chapter 8

Antirheumatic Agents

Inflammatory disorders, including arthritis and rheumatism, are a major cause of suffering in the world. In Ayurveda, several plants have been used to treat inflammation, rheumatism, and arthritis. Traditionally, these are used in combination for treatment, rather than as single drugs. Pharmacological testing has been carried out, and over 69 plants have shown encouraging activity as anti-inflammatory agents, while 27 have shown definite anti-inflammatory activity. Of these, seven have been clinically studied: *Boswellia serrata*, *Commiphora mukul*, *Curcuma longa*, *Semecarpus anacardium*, *Tinospora cordifolia*, *Vitex negundo*, *Withania somnifera*, and *Zingiber officinale*.

RHEUMATOID ARTHRITIS

Inflammation of the joints, or arthritis, covers many kinds of disorders characterized by pain, swelling, and stiffness of the joints, of which the most common is rheumatoid arthritis, afflicting 2-3 percent of the population. It is a chronic disorder affecting fingers, wrists, toes, and other areas of the body. It is still not certain as what causes the disease. According to modern medicine, various factors, including infection and autoimmune disorders, are considered to play a major role in causing this disease.

In Ayurveda, poor digestion is considered the root cause of all disease. An impaired digestion leads to the formation of *ama*, which gets deposited at various locations, such as the joints, leading to pain

and swelling of the joints. The disease entity *amavata* described by Caraka corresponds most closely to rheumatoid arthritis, and attempts have been made to verify this concept of the cause of this disease owing to faulty digestion by treating patients with digestive stimulants such as ginger, which aid digestion and absorption. See under *Zingiber officinale* in this chapter.

Boswellia serrata Roxb. ex Coleb. (Family: Burseraceae)

Boswellia serrata (see Plate 2 in color gallery) gum resin contains the pentacyclic triterpene acids—boswellic acids—that have been shown to be powerful inhibitors of leukotrienes, which play a major role in the cause and perseverance of inflammation in diseases such as arthritis, asthma, ulcerative colitis, Crohn's disease, etc. In addition, it also inhibits the enzyme elastase and the enzyme C-3 convertase of the complement system; these have been summarized in Chapter 3, "Gastrointestinal agents."

Details of the clinical studies were taken from abstracts, interviews, and reports of conferences, since there are few published papers. The first trials were exploratory in nature and were conducted on 20 patients,¹ and then later extended to cover a total of 175 patients² in the age group of 10-50 years, who had been suffering for the past 1-6 years from various musculoskeletal rheumatic disorders of moderate to severe intensity, including rheumatoid arthritis and ankylosing spondylitis, and who had earlier been treated with various antirheumatic drugs. Of the 175 patients, 122 were either bedridden or incapacitated from doing normal work and suffered from morning stiffness. These patients showed relief in presenting symptoms 2-4 weeks after starting the treatment. When 17 of these patients were put on placebo, symptoms recurred within 10 days. Out of the remaining 53 patients, 35 showed good results, whereas 18 did not show any appreciable response within a week of starting the treatment. None of the patients complained of any side effects.

In an open and double-blind cross-over study at the Government Medical College, Patiala, India, 30 patients were selected based on the criteria enumerated by the American Rheumatic Association and were treated with 200 mg of Boswellic acids thrice daily for 8 weeks.

The arthritic score—which determines the severity of rheumatic complaints—the erythrocyte sedimentation rate (ESR), and the rheumatoid factor were checked after 14 days. Supplementary analgesics such as diclofenac sodium were required for the first 2 weeks but could be stopped subsequently. There was significant improvement in morning stiffness, tenderness, and swelling of various joints and in restored function. Significant improvements were also seen in the ESR and the arthritic score. In long-term studies of more than a year, the acceptability of the drug was found to be good with no side effects seen.^{3,4} Similar results were observed in 60 patients.⁵

Patients with long-standing rheumatoid arthritis showing inflammatory activity despite medication were included in two placebo-controlled studies and the results were evaluated for 81 patients: 39 on the drug and 42 on placebo. Joint swelling, joint pain, ESR, C- reactive protein as indicator of inflammation, morning stiffness, patients' estimation of pain, their general condition, as well as the use of anti-inflammatory drugs were evaluated before therapy, and after 6 and 12 weeks. There was marked improvement in all the investigated parameters in the *Boswellia* group as compared to the placebo group.⁶

In a published survey of a number of open and placebo-controlled trials in 260 patients with rheumatoid arthritis, the effect of administration of special extracts of *Boswellia serrata* H15 consisting of 400 mg tablets given as a dosage of 3 tablets twice or thrice daily was evaluated by using different approaches in the different trials. The basis for evaluation included joint swelling, pain, ESR, morning stiffness, additional anti-inflammatory drugs required, side effects and tolerance to therapy. It was found that the drug produced a significant reduction in swelling, pain, and morning stiffness. In addition, ESR was reduced and patients could reduce the intake of NSAIDS with the added advantage of improved health and well-being.⁷

In another double-blind pilot study, where 78 patients were recruited in 4 centers, the results of 37 patients available at one center has been published, which concludes that treatment with H15 did not show any measurable difference when compared with placebo, and further studies with larger patients numbers are required.⁸ However, it is interesting that patients received a high dose (3,600 mg), much

above that used in earlier positive trials. Further studies including dose-searching studies need to be carried out.

Information on safety on *Boswellia serrata* is covered in Chapter 3, “Gastrointestinal agents.”

***Commiphora wightii* (Arn.) Bhandari (Family: *Burseraceae*)**

Latin: *Commiphora mukul* Engl,
Balsamodendron mukul Hook
 ex Stocks

Sanskrit: *Guggul*, Devadhoopa

Hindi: *Guggulu*, *Guggul*

Tamil: Maishaki Gukkal

English: Indian Bdellium

Commiphora mukul (*Commiphora wightii*) (see Plate 7 in color gallery) is better known for its hypolipidemic effect as a result of the scientific work carried out on it, but in Ayurveda, several combination preparations of the purified gum resin of the tree with other herbs are used for the treatment of rheumatic disorders. More details regarding the plant, purification, and other aspects of its chemistry are available in Chapter 6.

A number of studies have been carried out to establish the anti-inflammatory activity of gum *guggul*. The gum resin has been shown to exhibit anti-inflammatory activity⁹⁻¹¹ comparable to hydrocortisone and butazolidine,⁹ and partially comparable to indomethacin and dexamethasone in experimental animals, the activity being seen in the acidic fraction of the resin.¹² The steroidal component of fraction A, obtained by petroleum ether extraction of the resin, showed a pronounced antiarthritic effect, better than phenylbutazone and comparable to hydrocortisone¹³ and hydrocortisoneacetate.¹⁴ In rheumatism, produced by using killed mycobacterial adjuvant in experimental animals, *Commiphora mukul* gum fraction A was found to be as effective as phenylbutazone and ibuprofen in reducing joints swelling.¹⁵ The aqueous extract of gum *guggul* showed significant anti-inflammatory activity reducing maximal and total edema response in carrageenan-induced rat paw edema.¹⁶ Gum *guggul* lipid extract was evaluated in both acute and chronic models of inflammation and was

found active only in Freund's adjuvant-induced model; however, the doses used, that is $250 \text{ mg}\cdot\text{kg}^{-1}$, caused considerable morbidity and mortality in infected animals but not in the healthy ones.¹⁷

Rheumatoid arthritis

Very few clinical studies have been carried out on *Commiphora mukul* as a single drug for rheumatism, and these have been of a preliminary nature. Dose-requirement studies carried out with purified *guggul*, on 35 patients suffering from rheumatoid arthritis, assessed it to be a digestive and an analgesic agent based on its antirheumatic activity and its action on the ESR. Also to be evaluated were the side effects and the potential development of drug resistance.¹⁸

In another open study, purified *guggul* was given to 30 patients with rheumatoid arthritis. It was found that 66.66 percent of patients showed complete remission of the disease, 23.33 percent showed major improvement, and 10 percent showed minor improvement. The impression was that the drug had anti-inflammatory and analgesic properties.¹⁹

The petroleum ether extract known as fraction A was tried on human beings and found to have an anti-inflammatory effect at $500 \text{ mg}\cdot\text{kg}\cdot\text{day}^{-1}$.²⁰ In a randomized double-blind trial with 60 patients with confirmed rheumatoid arthritis, the disease modifying potential of gum *guggul* (group A) 500 mg capsules and a proprietary preparation known as Rhumayog with gold (group B) was tried against Auranofin (group C), which has been a standard drug in the therapy of chronic polyarthritis and psoriatic polyarthritis. It was found that the disease-modifying effect was seen in both group A taking *guggul* and group C taking Auranofin with statistically significant improvement in Ritchie index, degree of morning stiffness, and platelet aggregation; however, therapy with Auranofin is accompanied by many side effects such as diarrhea, skin eruptions, kidney damage, etc., and must be constantly monitored by a doctor.²¹

Osteoarthritis

Osteoarthritis is a common disease of the weight-bearing joints. The cartilage lining the joints degenerates due to wear and tear resulting in pain, stiffness, and sometimes loss of function. In Ayurveda,

this is called *sandhigatavata*. In another trial, 30 osteoarthritis patients with a score of 2 or more on the Kellegren-Lawrence scale, for at least one knee, were included in the trial. A dosage of 500 mg capsule of *Commiphora mukul* concentrated extract was given thrice a day together with food for 1 month after which there was a significant improvement in both primary and secondary outcome measures, and there was continued improvement in the primary outcome measure at the 2-month marker and also on further follow-up. No side effects were observed, and it was concluded that *Commiphora mukul* was a relatively safe drug to reduce symptoms of osteoarthritis.²²

Spondylosis and sciatica

In open trials, the effect of purified *guggul* (4 g·day⁻¹ in three divided doses) for 21 days has also been tried out in patients of cervical spondylosis (affecting joints between vertebrae in the neck) and ankylosing spondylitis (affecting spinal vertebrae and the sacrosiliac joints). A total of 22 patients took part in the cervical spondylosis trial and 17 in the ankylosing spondylitis trial. The effect of purified *guggul* alone was compared with the effect of a preparation of fresh *Vitex negundo* leaves fried in oil and applied externally for 15 minutes, and that of the combined effect of *guggul* and the fried-leaf preparation in a few patients in the three groups. The combination offered greater symptomatic relief in both cervical spondylosis and ankylosing spondylitis; however, pain relief was better with *guggul*.^{23,24} The response to *guggul* was poor in patients with ankylosing spondylitis. In patients with sciatica (pain along the sciatic nerve affecting buttocks and thighs, and sometimes extending down the leg and the foot), when *guggul* was administered along with *katibasti* treatment (soaking the area with hot oil for 15-40 minutes), it was found to be very effective.²⁵

Plant combinations

The clinical effects of combinations of *guggul* with ginger (*sunthi*) in rheumatoid arthritis, and the clinical effects of combinations of *guggul* with other herbs like *Dalbergia lanceolaria* and *Semecarpus anacardium* in osteoarthritis, frozen shoulder, and sciatica have been

studied and found to be more effective than the individual herbs alone.²⁶

Considering the importance of *Commiphora mukul* in the treatment of rheumatic disorders in Ayurveda, there is a paucity of clinical data to emphasize its importance. In addition, the age of the resin, composition of the drug, and its efficacy profile in different rheumatic conditions needs to be worked out. Further, experimental studies to find out the mechanism of action of the drug are also required.

Information on the safety of *guggul* is covered in Chapter 6, “Cardiovascular drugs.”

***Curcuma longa* L. (Family: Zingiberaceae)**

Latin: <i>Curcuma domestica</i> Valeton	Hindi: Haldi
Sanskrit: Haridra	Tamil: Manjal
English: Turmeric	

Turmeric has been used internally²⁷ and externally²⁸ for its anti-inflammatory properties since the time of Caraka and Susrutha. Turmeric has traditionally been used in India for a variety of ailments, including digestion due to its choleric activity—see Chapter 3, “Gastrointestinal agents”—and for the management of asthma—see Chapter 5, “Respiratory tract drugs.” The other important properties that have been scientifically investigated include its antioxidant, anticancer, immunostimulant, and antiviral properties. The rhizome is an official drug in the *Indian Herbal Pharmacopoeia*, 2002, for its anti-inflammatory, stomachic, and tonic properties.²⁹

Other aspects of turmeric, including distribution and chemical constituents, are covered in Chapter 3, where it is first discussed. The pharmacology of turmeric has been extensively reviewed,³⁰⁻³⁶ and turmeric has been shown to possess anti-inflammatory properties in the various models, including acute, subacute, and chronic models of inflammation. In an experimental study, examination of petroleum ether, alcoholic extract, and aqueous extract of turmeric showed that the aqueous extract was the most active when administered

intraperitoneally in an acute model. The essential oil and the curcumins are considered to be among the active constituents showing anti-inflammatory activity. Administration via the intraperitoneal route produces better anti-inflammatory activity when compared to the oral administration of the crude drug powder, owing to the poor absorption of curcumin.³¹ However, the serum concentration, extent of absorption, and bioavailability of curcumin can be increased severalfold by coadministration of curcumin with piperine, which is a bioavailability enhancer. Thus, in human volunteers when 2 g curcumin was coadministered with 20 mg of piperine there was a 2,000 percent increase in bioavailability of curcumin.³⁷

Curcumin has been shown to inhibit a number of different molecules involved in inflammation.³⁶ It has been shown to inhibit prostaglandin synthesis,³⁸ cyclooxygenase,³⁹ and lipoxygenase.⁴⁰ Curcumin is also a natural inhibitor of the COX-2 enzyme. Drugs showing COX-2 inhibition are currently being advocated by pharmaceutical companies because of their relative lack of side effects on the gastrointestinal system. Curcumin has been shown to inhibit the release of both COX-1 and COX-2 enzymes; with better inhibition of the COX-2 enzyme.⁴¹ The relatively weaker action on COX-1 reflects the better GI tolerance of curcumin.

In a randomized double-blind placebo-controlled study in dogs with osteoarthritis of the canine elbow, or hip, an extract of *Curcuma longa* (*domestica*) and *Curcuma xanthorrhiza* or placebo was given twice daily for 8 weeks. The test preparation was received by 25 dogs, whereas 29 received the placebo. Although there was no difference in the peak vertical force, the overall assessment of the efficacy of the investigators was statistically significant; the owner's assessment was short of statistical significance.⁴²

There have been no reported trials using the whole drug. However, curcumin has been tried out in studies with small numbers of patients of rheumatoid arthritis. Considering the potential of the drug, further clinical studies are required.

In a double-blind, cross-over short-term study for 2 weeks, the anti-rheumatic activity of 1,200 mg·day⁻¹ curcumin was evaluated against 300 mg·day⁻¹ of phenylbutazone in 18 patients with rheumatoid arthritis. There was significant improvement in morning stiffness, walking

time, and swelling of the joints after 2 weeks of oral curcumin therapy. Neither any side effects nor any change in grip strength, articular index, or ESR was observed in either of the two groups ascribed to the short period of administration.⁴³ In a continuation of the same trial, the number of patients was increased to 31 and the dose levels were increased to 1,800-2,100 mg-day⁻¹ and given for longer periods of 5-6 weeks;³⁰ however, more details are not available. There was significant improvement in all patients.

Similarly, not much detail is available regarding the effect of 1,500 mg-day⁻¹ curcumin on patients with osteoarthritis for 4-6 weeks, apart from the reported subjective improvement by the few patients on whom it was tried.³⁰

In a double-blind study the effect of 400 mg of oral curcumin given thrice a day for 6 days to patients with postoperative inflammation (hernia or hydrocele) was studied along with oral antibiotic—ampicillin. Phenylbutazone 100 mg given thrice a day served as the reference drug. Parameters evaluated were spermatic cord edema and tenderness, postoperative pain, and tenderness, which were added to arrive at a total intensity scale. Curcumin was found to significantly reduce the total intensity score (2.38) as compared to placebo (1.0), which was comparable to the effect seen with phenylbutazone (1.57).⁴⁴

Further clinical studies are needed to arrive at the utility of turmeric and curcumin in different conditions; the safety of turmeric and curcumin is covered in Chapter 3.

***Semecarpus anacardium* Linn. f (Family: Anacardiaceae)**

Sanskrit: Bhallataka	English: Marking nut, Oriental cashew
Hindi: Bhilawa	Tamil: Senkottei

Semecarpus anacardium is a medium-sized, deciduous tree found throughout the hotter parts of India and in the outer Himalayas.⁴⁵ The official part of the plant is the fruit, and the fruit is a very powerful drug belonging to the group of toxic materials used in

Ayurveda. Therefore, it is used only after processing to make it suitable for consumption. After processing it is considered a rejuvenative (*rasayana*) with very powerful antiaging effects. The oil from the fruit and the juice from the bark of the tree have vesicant action said to affect sensitive people even at a distance, so that people are often afraid even to approach the tree.⁴⁶ The Sanskrit name *bhallataka* is derived from *bhalla* or spear. It is also one of the most heat-generating herbs used in Ayurveda, and therefore called *agni* or *analla*, in Sanskrit, which denotes fire. Because of this heat-producing property, there are restrictions for its use in hot weather: by pregnant women, the elderly, and the very young. Its use is also contraindicated in people of a *pitta* constitution, that is, those people who already have a lot of “heat” in their body. In addition, the drug is often administered with milk, clarified butter, or with butter products that are considered to mitigate the heating effects of the drug. Thus it is a drug that is to be taken only under supervision of a competent doctor using carefully processed, detoxified material.⁴⁷ The English name “marking nut” refers to the use of the black vesicant oil present in the fruit for marking clothes by washermen.⁴⁵ When used appropriately *bhallataka* helps in a number of disease conditions, including digestive disorders, piles, rheumatism, and cancer.

The fruits contain anacardic acid, aromatic amines, and about 32 percent of vesicant oil—the major constituent of which was termed bhillanol and later shown to be a mixture of phenolic compounds consisting of more than seven carboxylic acids. Also present are numerous biflavonoids—including tetrahydroamentoflavone, tetrahydrorobustafavone, and galluflavanone—and several amino acids.^{45,48}

Pharmacological screening of the nut-milk extract^{49,50} and the chloroform extract^{51,52} have shown that they exhibit anti-inflammatory activity in a number of experimental models of inflammation. In adjuvant-induced arthritis in albino rats the milk extract was effective at a dose level of 150 mg·kg⁻¹.⁵⁰ The drug may be acting by reducing lipid peroxidation,⁵³ its potent antioxidant activity,⁵⁴ by stabilizing disrupted lysosomal enzymes,⁵⁵ and at the same time normalizing carbohydrate metabolism, which is affected during adjuvant arthritis.⁵⁶ In addition, aqueous extract of *Semecarpus anacardium* shows moderate analgesic effect.⁵⁷

Rheumatoid arthritis

In a trial with 140 rheumatoid arthritis patients, 20 patients on placebo were kept as control, whereas 120 patients were given the milk decoction of *Semecarpus anacardium* nuts for 27 days. Patients were evaluated on the basis of clinical and functional improvement and ESR levels. In addition, gastrointestinal function was evaluated on the basis of D-xylose absorption tests. Sixty-five percent of patients experienced very good relief in symptoms and improvement in walking time, pressing power, grip power, etc. Improvement was also seen in ESR, hemoglobin Hb, and D-xylose. More side effects were observed in female patients than in male patients.⁵⁸ In another open trial carried out on patients with rheumatoid arthritis (*amavata*), who were on *Semecarpus anacardium* pills, or *bhallatakavati* (*vati*: pills in Sanskrit), the improvement was assessed as being “spectacular.”⁵⁹

Whole *bhallataka* nuts (endocarp and pericarp) prepared with condensed milk solids (*khoya*) and sugar were given twice a day in 5-10 g doses (10 g equivalent to 1 nut) to 25 patients with rheumatoid arthritis. Forty percent of patients showed complete remission, while 40 percent showed major improvement, and 20 percent were assessed as showing minor improvement based on the criteria enumerated by the American Rheumatic Association. Improvement was seen in body ache, general malaise, and debility; improvement in appetite, food consumption, and in hemoglobin values; in ESR values in various functional tests like walking time, dressing time, articular strength, grip power, etc.⁶⁰

In another trial, the effect of *Semecarpus anacardium* nut-milk extract was evaluated on the basis of its effect on lysosomal enzymes, which are elevated in patients with rheumatoid arthritis. Treatment showed a decrease in the lysosomal enzymes leading the authors to conclude that the milk extract was a promising drug for rheumatoid arthritis. No side effects were observed and the drug was well tolerated. One patient had urticaria, which disappeared on reduction of the dose from 5 g to 2.5 g.⁶¹

In a placebo-controlled study, 40 patients were enrolled in the trial: 30 in the drug group and 10 in the placebo group. The drug consisted of 3-5 g of *amrit bhallataka* twice daily with milk together with

500 mg of *Boswellia serrata* (*sallaki*) gum in capsules taken thrice daily for 10 weeks. It was found that 60 percent of patients receiving the drug showed very good change in laboratory findings and in clinical improvement, with eight patients showing normal improvement and four patients showing no improvement. Unfortunately, no other details are available since the trial was reported as an abstract.⁶²

A three-drug combination of *Semecarpus anacardium* (*bhallatak*), *Dalbergia lanceolaria* (*gourakh*), and *Commiphora mukul* (*guggulu*) has already been covered under *Commiphora mukul* earlier in this chapter. This combination has been shown to be better than the individual herbs for rheumatoid arthritis, sciatica, frozen shoulder, and osteoarthritis.

Sciatica

In an open trial, 42 patients with sciatica (*gridhrasi*) were given *Naimittika rasayana* containing purified *bhallataka* in dosages of 100 mg to 1,000 mg twice a day. The *Naimittika rasayana* regimen consists of increasing the dosage every day by 100 mg starting from 100 mg and going up to 1,000 mg after which it is again reduced to 100 mg for 2-12 weeks with milk and ghee. Twenty-five patients were completely relieved of their complaints, although 12 patients experienced partial relief. Also observed was an overall improvement in their physical condition. Side effects were observed in five patients when the dosage was increased to more than 500 mg.⁶³

In a dose-searching study conducted with purified *Semecarpus anacardium* (*bhallataka*), good results were obtained at the 4 g·day⁻¹ dosage, which was judged to be the optimum dosage for treatment of sciatica.⁶⁴

As mentioned earlier in the opening paragraph, the drug is toxic before processing, but after suitable treatment it is considered non-toxic. There is an irritant oil in the pulp of the fruit that needs to be removed or modified.⁴⁶ Thus, a chloroform extract of the nuts of *Semecarpus anacardium* was toxic at all dose levels tested (50-400 mg·day⁻¹).⁶⁵ However, a milk extract of the nuts did not show any acute toxicity (72 hours) at the levels tested (75-2,000 mg·day⁻¹). In the subacute toxicity (30 days) no marked alteration was observed in blood and biochemical values at 50-500 mg·day⁻¹ body weight.

However, at 500 mg·day⁻¹ there was an increase in blood glucose, serum creatinine, uric acid, and blood urea. In addition, changes in lipid profile were observed owing to the fact that clarified butter (ghee) is used as the base. Vital organs showed normal architecture.⁶⁶ The clinical toxicity of the nuts studied in 266 patients showed no toxicity or side effects.⁶⁷ In a trial on the role of *Semecarpus anacardium* on the management of rheumatoid arthritis, side effects such as urticarial rashes, mucosal irritation, and bleeding were seen. The patients in this trial were carefully monitored and the drug withdrawn, if needed.⁵⁸ In another trial, the drug prepared by boiling first in water then adding the solidified milk known as *khoya*, prepared by boiling off the water, was well tolerated, with only one patient developing urticaria, which disappeared at half dose and the drug was well tolerated.⁶⁰

***Tinospora cordifolia* (Willd.) Miers ex Hook f. & Thoms.
(Family: Menispermaceae)**

Tinospora cordifolia (see Plate 4 in color gallery) is a climber found throughout India growing on trees and shrubs. The stem and the aerial roots are generally used fresh. Other aspects of the plant are covered in Chapter 4, “Hepatoprotective agents” where the herb is first described. It is one of ten plants commonly used in preparations for the treatment of joint diseases.^{68,69} The stem is an official drug in the *Indian Herbal Pharmacopoeia*, 2002, as an analgesic and an antipyretic agent.⁷⁰

Experimental studies on small animals have demonstrated the anti-inflammatory effects of the aqueous extract of *Tinospora cordifolia* in acute and chronic inflammation.⁷¹⁻⁷⁴ In experimental adjuvant-induced arthritis it inhibited both phase I and II.⁷³ The aqueous extract at 1 g·kg⁻¹ showed maximum anti-inflammatory effect in cotton pellet granuloma and formalin-induced arthritis.^{74,75}

In an open trial, 50 patients with various joints problems diagnosed according to Ayurveda as *amavata* (usually equated as rheumatoid arthritis in modern parlance) and *sandhigatavata* (usually equated as osteoarthritis in modern parlance), degenerative arthritis, senile arthritis, and psoriatic arthritis were treated with capsules containing 480 mg of a dried aqueous extract of *Tinospora cordifolia*.

The results were assessed in 24 patients as showing complete relief, 16 with partial relief, and 10 patients with no relief at all. Good improvement was seen within 10 days of starting the treatment in 72 percent of cases with the drug being well tolerated. In addition, many patients obtained relief from constipation.⁶⁹

Other trials with *Tinospora cordifolia* on patients with rheumatoid arthritis have been reported either as a single drug⁷⁶ or in combination with ginger,⁷⁷ which is covered under the section on ginger.

The safety of *Tinospora cordifolia* is covered in Chapter 4, “Hepatoprotective agents.”

***Vitex negundo* Linn. (Family: Verbenaceae)**

Sanskrit: Nirgundi, Sinduwar	Tamil: Nochi
Hindi: Sambhalu	English: Five-leaved chaste tree

Vitex negundo is a large aromatic shrub commonly found growing in many parts of India.⁷⁸ The Sanskrit name *nirgundi* implies that it works against a number of ailments (*nir*: no; *gunda/gundi*: notorious). There are two varieties available in India that differ in the color of the stems—white (*Vitex negundo* var. *negundo*), because it is covered with white hair, and purple (*Vitex negundo* var. *purpurescens*); however, it is not clear from published literature which variety has been used in studies. Although all parts of the plant are used, the leaf and root are commonly used in medicine; however, the leaf is used widely. The leaves are used both internally and externally to treat joints swellings and pains, rheumatism, fever, cough, and sinus problems.⁷⁹

The leaves contain approximately 0.04-0.07 percent of an essential oil containing several terpenes (with β -caryophyllene as the major constituent), flavonoids (casticin, orientin, isoorientin, luteolin, luteolin-7-O-glucoside, corymbosin, gardenins A and B, etc.), flavanones, several iridoid glycosides (aucubin, agnuside, nishindaside, negundoside, 6'-p-hydroxybenzoyl-mussaenosidic acid), alkaloids (nishindine and hydrocotylene),^{78,80} betulinic acid, and ursolic acid.⁸¹

The leaf and leaf extracts (petroleum ether, methanol, aqueous methanol, and water) also showed significant analgesic activity.⁸²⁻⁸⁶

The leaves have been shown to have anti-inflammatory activity in a number of experimental models.^{83,86-88} The leaves have also been shown to have antiarthritic activity in rats.⁸⁹

The anti-inflammatory effect of *Vitex negundo* leaves is considered to be mediated through histamine and 5-hydroxytryptamine (5-HT) both in the initial phase and in the delayed phase.⁹⁰ In addition, it has been suggested that the anti-inflammatory and analgesic effects may be due to the inhibition of prostaglandin synthesis,^{83,86} membrane stabilizing, and antioxidant activity.⁸⁶

In an open trial, 50 cases with rheumatoid arthritis were treated with *Vitex negundo* and found to show encouraging results.⁹¹ In another open trial on 30 patients with deranged “*vata*” described as “*vatavyadhis*” (problems with motion), which could be loosely considered to be rheumatism, 10 patients had rheumatoid arthritis (*amavata*), whereas 10 patients had osteoarthritis (*sandhigatavata*) and were treated with 1 g *Vitex negundo* leaf powder taken orally twice a day, while an oil extract of the leaves—prepared by boiling a decoction of the leaves in sesame oil till the water evaporated—was used to massage the affected areas. Five patients in each group with rheumatoid arthritis and osteoarthritis received *Commiphora mukul* orally and served as control. Patients had the disease for periods ranging from 1 to 10 years. Of the ten patients on *Vitex* with rheumatoid arthritis, four patients showed improvement ranging from 25 to 50 percent based on clinical parameters, lowering of leukocytosis and improvement in ESR values after 3 months, whereas no improvement was seen in the remaining six cases even after 6 months, and the medication was changed to *Commiphora mukul*. In the control group all the five patients showed improvement, two cases recovering fully, one with 75 percent improvement, another with 50 percent, and the remaining patient dropping out due to loose motions as a result of *guggul* treatment. In the group with *sandigata vata* (osteoarthritis) all the ten patients using *Vitex* showed improvement based on lessening of pain, decrease in swelling, and clinical improvement. No side effects were observed. In two cases that were followed using X-ray, there was no radiological improvement. In the *guggul* group improvement was not as good as the trial group.⁹² Thus *Vitex negundo* was found more effective in noninflammatory cases, such as

osteoarthritis (*sandhigata vata*), whereas *Commiphora mukul* worked better in patients with rheumatoid arthritis (*amavata*). In addition, *Vitex negundo* was considered useful in cases where *Commiphora mukul* caused gastric irritation and diarrhea.⁹²

However, the numbers in both arms are small and the patient population appears to have been nonhomogenous. Further trials are warranted with larger patient numbers and standardized plant material considering the promising nature of the results.

Sciatica

In a trial of 20 patients with sciatica, 10 patients were treated with *sodhana*, which includes certain Ayurvedic “purificatory” procedures for detoxification and *samana* (drug treatment), and 10 patients were treated with *Vitex negundo* and *Commiphora mukul* (*samana* alone). In group I, 60 percent of patients had complete relief and 40 percent had marked relief; however, in group II, 40 percent had complete relief, 40 percent had marked relief, and 20 percent had mild relief.⁹³

The combination of *guggul* and *Vitex negundo* has been tried out both in ankylosing spondylitis and in cervical spondylosis; see *Commiphora mukul* earlier in this chapter. Another combination *rasonadi kwath* using garlic, ginger, and *nirgundi* (*Vitex negundo*) in rheumatoid arthritis has been tried out.⁹⁴ Fifty patients were included in the trial based on the American Rheumatic Association 1959 guidelines. A decoction made from equal parts of dried ginger, garlic, and *Vitex negundo* was given daily at a dose of 25 ml thrice daily for 6 weeks. The daily dosage corresponded to 25 g each of the three ingredients. Initially, acute pain was controlled both by oral Ayurvedic medication and external application as required. Results were assessed based on pain relief, diminishing of swelling and tenderness, and increase in freedom of movement of joints, functional tests, and ESR. There was significant relief in swelling and pain in the joints in 2-3 weeks. Improvement in functional tests and ESR was also seen. Most patients were assessed as having “complete relief” or “partial relief.” Patients having the disease for a shorter time had greater relief.⁹⁴

The leaves are well tolerated in clinical dosages.⁹⁵ In an experimental study using fresh mature leaves of *Vitex negundo*, no acute toxicity or stress was found up to 5 g·day⁻¹ body weight.⁸⁶

***Withania somnifera* Dunal. (Family: Solanaceae)**

Sanskrit: Ashwagandha	English: Winter Cherry
Hindi: Asgandh	Tamil: Ammukara

Withania somnifera is an erect shrub found growing wild throughout the hotter parts of India and cultivated for its roots, which are well known in Ayurveda for their rejuvenative or *rasayana* properties. The roots are considered to have the smell of a horse, as the Sanskrit name *ashwagandha* denotes (*ashwa*: horse; *gandha*: smell), and are said to confer upon the person consuming them the strength and vitality of a horse. The roots are thus used in debility and convalescence—by sportspeople to increase endurance; in cough and sore throat; for reducing glandular swellings; as a sedative—for insomnia; and in rheumatism and gout.⁹⁶ *Ashwagandha* is commonly referred to as “Indian Ginseng” because of its beneficial properties. The root has an official status as an adaptogen in the *Indian Herbal Pharmacopoeia*, 2002.⁹⁷

The roots contain 0.2-0.3 percent of alkaloids and withaferin A together with several withanolides, which are C-28 steroidal lactones of the ergostane type.^{97,98} In addition, the roots contain starch, reducing sugars, hentriacontane, and a number of amino acids.⁹⁸ Also present are sitoindosides VII and VIII, which are acylsterylglucosides and sitoindosides IX and X, which are C-27 glycowithanolides that may contribute to the adaptogenic property displayed by *Withania somnifera*.⁹⁹

Withania somnifera root powder,¹⁰⁰ root methanol extract,¹⁰¹ and its active principles—a mixture containing equimolar concentrations of withaferin A and sitoindosides VII-X¹⁰²—were shown to possess antioxidant activity, which may explain the antistress, anti-inflammatory, immunomodulatory, and cognition-enhancing and rejuvenative effects shown in experimental and clinical studies. Withaferin A has been shown to have anti-inflammatory and antiarthritic property in several experimental models.¹⁰³

The roots of *Withania somnifera* have been shown to possess anti-inflammatory activity in acute, subacute, and chronic models of inflammation. In experimental animals, the powdered root showed

considerable anti-inflammatory activity, although less than phenyl butazone at $1 \text{ g}\cdot\text{kg}^{-1}$ body weight, while showing greater effect on acute phase reactants,¹⁰⁴ which are released into the blood during the acute phase of inflammation. NSAIDS have only a poor control of acute phase reactants in contrast to steroidal anti-inflammatory drugs. *Ashwagandha* in doses of $100 \text{ mg}\cdot 100\text{g}^{-1}$ body weight of rat showed a 32 percent reduction of paw volume as against 46 percent shown by phenyl butazone. In addition, *ashwagandha* influences most of the acute phase reactants in a very short time.¹⁰⁴ It has, especially, a good lowering effect on alpha-2 macroglobulin, an acute phase reactant, which is considered a sensitive index of the efficacy of anti-inflammatory drugs.¹⁰⁵ At a dose of $1 \text{ g}\cdot\text{kg}^{-1}$ it produced significant anti-inflammatory effect in cotton pellet granuloma in rats.¹⁰⁶ When tested for its long-term effect on adjuvant-induced arthritis in rats, it was found to exert a beneficial effect on swelling, and also prevented weight loss and degenerative changes seen in the bones in long-standing arthritis.¹⁰⁷

In carrageenin-induced paw edema,¹⁰⁸ the aqueous extract of *Withania somnifera* acts as an anti-inflammatory by blocking histamine H_1 and H_2 and 5-hydroxytryptamine receptors in the early phase and prostaglandin synthesis in the delayed phase of inflammation. However, in cotton pellet granuloma, the anti-inflammatory activity of *Withania somnifera* is mediated by blocking the H_2 receptors.¹⁰⁶

In an open, exploratory trial with 63 patients with various arthropathies, 46 patients with rheumatoid arthritis were given 4, 6, or 9 g of *Withania somnifera* root powder orally for a period of 3-4 weeks. It was found that pain and swelling disappeared in 12 patients; there was considerable improvement in 10; mild improvement in 11; 4 patients had no relief; and there were 7 dropouts.¹⁰⁹

In another open trial, 77 patients with rheumatoid arthritis (*amavata*) were treated with 3 g of *Withania somnifera* root powder thrice a day with milk for 6 weeks. The results were evaluated as "good" in 22 percent, "fair" in 53 percent, "poor" in 22 percent, whereas 3 percent did not respond. It was observed that patients who had the disease for less than a year responded better to the treatment.¹¹⁰

In a comparative randomized trial using three different treatment options, 120 patients with rheumatoid arthritis were assigned randomly to

receive *Cyperus rotundus* (*musta*) powder, *Withania somnifera* (*ashwagandha*) powder, or *Panchakarma* treatment consisting of various treatment modalities (such as vomiting, two forms of enema or bloodletting and enema, purgation, and nasal application of medicine) for detoxification. All three arms gave highly significant results ($p < 0.001$); however, maximum improvement was seen in the *Panchakarma* group.¹¹¹

In a preliminary open trial, 25 patients with radiologically confirmed cervical spondylosis were administered 4 g of *Withania somnifera* powder along with 100 ml of decoction from *Smilax china* given thrice a day for 30 days. The results were compared with brufen—an allopathic NSAID.¹¹²

In clinical trials for arthritis, using up to 6 g of *Withania somnifera* root powder for 3-4 weeks was well tolerated.¹⁰⁹ In a long-term trial on healthy volunteers in the age group of 50-59 years to study its tonic antiaging effect, 3 g of the root powder in three divided doses for 1 year showed no untoward side effects, and there was an increase in hemoglobin levels in the subjects.¹¹³ Acute toxicity and a 4-week subacute study with aqueous extract of *Withania somnifera* in doses from 50 mg to 1 g·kg⁻¹ showed no toxic effects. There was no hepatic or renal toxicity.¹¹⁴ Also chronic feeding of *Ashwagandha* at 100 mg·kg⁻¹ for 180 days did not show any toxicity or significant changes in the biochemical profile of blood;¹¹⁵ the safety data on *Withania somnifera* has been summarized.¹¹⁶

***Zingiber officinale* Roscoe (Family: Zingiberaceae)**

Ginger is a widely used traditional medicine for a variety of ailments, including its use for specific action in rheumatism and inflammation. Other aspects of the rhizome and its pungent principles have been covered in greater detail in Chapter 3, “Gastrointestinal agents,” where it first appears in this book. According to Ayurveda, impaired digestion is a major cause of all diseases, and ginger is considered to act on all the three phases of digestion—digestion, absorption, and elimination, and therefore help in ameliorating various problems. In Chapter 3, the use of ginger in relieving malabsorption—a contributory factor in the causation of inflammatory disorders, such as rheumatoid arthritis—has been described. Ginger is an

official drug in the *Indian Herbal Pharmacopoeia*, 2002, for its carminative, antiemetic, and anti-inflammatory properties.¹¹⁷

Ginger exhibits an anti-inflammatory effect in carrageenan-induced paw edema¹¹⁸⁻¹²¹ and in cotton pellet-induced granuloma in rats.¹²⁰ Ginger oil has been shown to exhibit anti-inflammatory activity inhibiting chronic adjuvant arthritis in rats.¹²² More specifically, the gingerols and shoagols are among the active constituents of ginger.¹²³ 6-Gingerol and four other compounds, namely, [6]- and [10]-dehydrogingerdione, and [6]- and [10]-gingerdiones, were found to be potent inhibitors of prostaglandin biosynthesis.¹²⁴ Ginger and its various pungent constituents behave as dual inhibitors of the arachidonic acid pathway, inhibiting both cyclooxygenase^{125,126} and lipoxygenase.^{125,127,128} Of special interest is the inhibition of COX-2.¹²⁶ In addition, ginger extract¹²⁹ and gingerol¹³⁰ inhibit platelet aggregation, thromboxane synthase, and the incorporation of arachidonic acid into thrombocytes. [6]-Gingerol has also been shown to be a potent inhibitor of NO-synthesis, and is effective in protecting against peroxynitrite-induced damage.¹³¹

One of the first studies using ginger was reported in 1977.¹³² In an open study, seven patients with rheumatic disorders given ginger found relief in pain and associated symptoms.¹³³ In a larger group of 56 patients, 28 with rheumatoid arthritis, 18 with osteoarthritis, and 10 with muscular discomfort, were treated with powdered ginger. Of these, 75 percent of arthritis patients found relief in pain and swelling. All patients with muscular discomfort had relief from pain. No side effects were reported during ginger administration in periods ranging from 3 months to 2.5 years.¹³⁴

A number of combinations of ginger with other drugs have been reported to study the effect of gastrointestinal stimulant drugs for the treatment of rheumatoid arthritis. Thus, four groups with three combination drugs were tried out. In group 1, ginger was combined with *Tinospora cordifolia*, in group 2 and in group 4 ginger was combined with *Commiphora mukul*, whereas in group 3 a decoction of the three plants of ginger, *Vitex negundo*, and *rasna* (Botanical name not mentioned) was tried out. In order to estimate the comparative efficacy of the drugs they were compared against standard Ayurvedic drugs that are traditional multiplant preparations commonly used in the treatment

of rheumatism—*Yogaraja guggulu*, *Vatagajankusha Rasa*/*Amavatari Rasa*, and *Maharasnadi Kwatha*. Patients were selected on the basis of the 1959 criteria of the American Rheumatic Association.

In the first trial, 77 patients were enrolled and given 25-50 ml of a decoction of *Zingiber officinale* (*sunthi*) and *Tinospora cordifolia* (*guduchi*) thrice a day or given the traditional formulations—*Yogaraj guggulu*, *Vatagajankusa rasa*, and *Maharasanadi kwatha*. There was slow improvement in the major presenting features (pain, swelling, and restriction in movement). The results from the *sunthi-guduchi* group were assessed to be better because more patients experienced partial relief, fewer patients had no relief, and there were fewer dropouts. The ESR showed significant decrease in the *sunthi-guduchi* group coming within normal limits at the end of the treatment period.^{135,136}

The second combination of ginger with *Commiphora mukul* (*guggul*) was tried out first in an open comparative format with 63 patients, of which 36 patients received 2 g of *sunthi-guggul* (1 g each of powdered rhizome of *Zingiber officinale* and purified resin of *Commiphora mukul*) thrice a day for 6 weeks, whereas the second group received the traditional combination of 1 g *Yogaraja guggulu*, 0.5 g *Amavatari Rasa*, and 25 ml *Maharasnadi Kwatha* thrice a day. Inclusion parameters were evolved based on the 1959 criteria of the American Rheumatic Association. These were morning stiffness, pain while passing motion, tenderness, swelling in one or more joints, and symmetrical joint involvement. Apart from clinical assessment, ESR levels were also monitored. The improvement in the *sunthi-guggulu* group was assessed as being “remarkable” and the number of patients obtaining complete relief and partial relief was more than the patients in the standard treatment group. However, the majority of patients had the disease for less than 1 year.^{135,137}

Based on the good results obtained with the combination of *sunthi-guggulu*, another trial with 75 patients was carried out for 6 weeks with the drug along with external treatment. All patients who completed the trial showed definite improvement although the number of patients who obtained complete relief was small; partial relief was obtained by more than 50 percent of patients. It was observed that male patients and those with a shorter duration of the disease showed better results.^{137,138}

The third group of 50 patients was treated for 6 weeks with 25 ml decoction of the combination containing *rasna* (Botanical name not mentioned), *sunthi* (*Zingiber officinale*), and *nirgundi* (*Vitex negundo*) taken thrice daily. Complete relief was experienced by 28 percent of the patients, whereas 46 percent had partial relief. It was observed that female patients had better relief; however, the patient number is perhaps too small to make definite conclusions and this observation needs to be confirmed.¹³⁵ The drug *rasna* has not been botanically identified in the paper by the Latin name, which is unfortunate considering the fact that *rasna* is one of the so-called controversial drugs of Ayurveda where the identity of the plant is disputed and more than one plant is considered to be the genuine source of the drug.

In a recent, randomized, double-blind, placebo-controlled, multicentric, parallel group study, the efficacy and safety of *Zingiber officinale* with *Alpinia galanga* was evaluated in 261 patients with moderate-to-severe knee pain because of osteoarthritis. The drug was a standardized and highly concentrated extract containing the two species. The primary efficacy criterion was a reduction in knee pain on standing. There was statistically significant reduction in symptoms of osteoarthritis of the knee (63 percent responders in the ginger group versus 50 percent in the placebo group). Patients receiving the ginger extract experienced more gastrointestinal side effects than the placebo group (59 versus 21).¹³⁹

The safety of ginger is covered in Chapter 3, "Gastrointestinal agents." In a trial using ginger in 56 patients for periods ranging from 3 months to 2.5 years no side effects were experienced.¹³⁴

Further clinical trials are needed to establish the efficacy in larger patient numbers, especially for the two combination preparations of ginger with *Tinospora cordifolia* and with *Commiphora mukul*, which appear to offer advantages over monotherapy.

NOTES

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Chapter 9

Skin and Trauma Care Agents

The skin, which covers an area of 2 m², is the largest organ in the body and, therefore, also subject to external influences such as heat and light; apart from numerous agents, for example bacteria, fungus, virus, etc.; physical damage due to accidents, cuts, wounds, burns; and—in the case of traumatic injuries—breaking of bones. In Ayurveda, plants have been the mainstay of treatment and the management of skin diseases, or *kustha*. In the field of traumatic injuries (methods of treatment and care of injury), there are experts who specialize in the setting of bones and the treatment of the injury. The hereditary bonesetters of Puthur, a small village in Andhra Pradesh, are well known for their bonesetting skills. Herbs are applied externally on the injured site, and are also given internally to help healing and strengthening of the bone. People come from far and wide to get their injuries treated.

A large number of plants have been found to be used in the treatment of skin disorders.¹ However, relatively few of them have been subjected to clinical trials although or perhaps because, they form part of the day-to-day practice of Ayurvedic physicians. Plants and plant products are frequently used in homes to preserve healthy skin. Common among these are turmeric and sandalwood. Others include neem leaves, the astringent barks of different *Ficus* species, and members of the Labiateae such as holy basil, *Leucas aspera*, etc.

This chapter is divided into three sections—the first section is on skin diseases and includes the different categories given by Willuhn. It covers diseases caused by external agents (Virus: *Shingles zoster*; Bacteria: Impetigo, *Pityriasis versicolor*; Fungus: ringworm; Mites:

Scabies), and those caused without an external agent, such as psoriasis, eczema, leukoderma, neurodermatitis, and allergic skin problems.² The second section covers herbs used in wound healing and the third section is on herbs used for healing of bones.

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SKIN DISEASES

Since most of the trials are of a preliminary and exploratory nature covering several indications, it is not possible to group them into different categories and they are covered according to the plant. Among various skin problems, eczema, scabies, and ringworm are commonly found in India. In addition, numerous skin disorders caused by fungi, bacteria, virus, or due to allergy also abound.

***Azadirachta indica* A Juss. (Family: *Meliaceae*)**

Latin: *Melia azadirachta* Linn.

Hindi: Neem, Nimb

Sanskrit: Nimba

Tamil: Veppan, Vembu

English: Margosa

Azadirachta indica or the *neem* tree is considered to be a veritable pharmacy, all parts being used for a wide variety of ailments, especially for the treatment of skin disorders of varied etiology. Just sleeping under a *neem* tree is said to promote one's health. Whereas all parts of the tree are used medicinally, the leaves and seed oil are used most widely for the treatment of skin diseases. The fresh green leaves have long been used as a household remedy to relieve itch in smallpox, chicken pox, and measles. It is also customary to apply a

freshly ground paste of turmeric and *neem* leaves on the body while taking the first bath after recovering from measles, chicken pox, and small pox. Other aspects of neem, its chemistry, and use in diabetes are covered in Chapter 11, "Antidiabetic agents."

There is evidence to show that *neem* is active against a wide range of bacteria, fungi, and viruses. The aqueous and alcoholic extract of the leaf and bark,¹ the chloroform extract of leaves, the seed oil, and the gum showed antibacterial activity against a variety of pathogens.²⁻⁵ The oil obtained by steam distillation of fresh mature leaves showed antifungal activity against *Trichophyton mentagrophytes*⁶ in vitro; stem bark extract⁷ and the ethanolic extract of seeds had antimycotic activity against *Candida albicans*.⁸ *Neem* leaf extract has also shown antiviral activity against several viruses. Water extract of tender leaves showed antiviral activity against vaccinia^{9,10} and variola⁹ viruses. In addition, *neem* leaf extract shows activity against fowl pox virus, chikungunya, and measles viruses, group B coxsackieviruses and dengue virus type-2.¹⁰⁻¹³

It has been suggested that the range of diseases on which *neem* has a favorable effect is owing to the immunomodulatory effect shown by several parts of the tree.^{14,15} Thus the bark,^{14,15} leaf,^{15,16} and seed oil¹⁷ have been shown to have an immunomodulatory effect. The leaf aqueous extract modulates both cell-mediated and humoral responses in mice.¹⁶ In addition, *neem* exerts an anti-inflammatory effect. Thus, the alcoholic extract of leaves¹⁸ and the water-soluble portion of the alcoholic extract,¹⁹ but not the ether soluble fraction,²⁰ show anti-inflammatory effect. However, the ether-soluble fraction has a potent analgesic effect under acute inflammatory conditions.²⁰

Eczema, ringworm, scabies

Eczema is an inflammation of the skin that is accompanied by itching, scaling, or blisters. Ringworm (tinea) is a fungal infection of the skin, hair, and nails; whereas, scabies is caused by the mite *Sarcoptes scabiei* that causes itching.

In an open study, patients with common skin disorders such as eczema, ringworm, and scabies were treated with a lotion prepared by dissolving the residue of a 70-percent alcoholic extract of neem leaves in propylene glycol in the ratio of 2:3 and applying it on the

affected part. The lotion was applied twice a day for 3 days to treat scabies, and 4-8 days to treat cases of ringworm. The lotion was found to be effective in all cases of acute weeping and chronic eczema, ringworm, and scabies.^{21,22} Many of these patients were nonresponding to conventional treatments, such as salicylic acid, benzoyl benzoate, and sulfur.

In an open trial, the oil obtained by boiling *Strychnos nux vomica* nut in neem oil was applied externally on patients with eczema and was found to yield good results.²³ In patients with scabies, a 4:1 mixture of fresh neem leaves and turmeric powder was applied on 814 patients with scabies. More than 97 percent of the patients were cured within 3-15 days by this treatment.²⁴ No toxic or adverse effects were seen. In a report, the use of one to two 500 mg neem capsules made from leaves, flowers, and twig powder, taken orally with food twice a day for long periods, “dramatically” helped patients with chronic fungal infections of skin and nails, boils, and other bacterial infections. It was also reported to be useful in cases of allergic skin conditions and psoriasis.²⁵ Other neem products that have been reported to be useful in psoriasis are the bitter compound nimbidin²⁶ and neem toddy²⁷ taken together with a compound herbomineral preparation *Arogyavardini vati*, which is used in a number of conditions—skin problems, obesity, hepatitis, chronic constipation, anorexia, heart problems, and many others. Studies involving the use of neem preparations in wound healing are discussed later in this chapter.

It would thus be worthwhile to explore the nature of the products required and conduct further trials to establish the efficacy parameters to confirm the success that has been reported with a variety of neem preparations.

Preparations derived from the neem tree, such as from the bark and the leaf, generally have a wide margin of safety except for the seed oil for which some data exists that it may be unsafe, especially in oral consumption by infants in doses of 5-30 ml,²⁸ which is in any case a high dosage for any oil to be given to infants. One study has shown that the seed oil is safe for topical use in wounds;²⁹ however, care needs to be taken in assessing the quality of the starting material, the method of processing, and the composition of oil derived from it.

Cardiospermum halicacabum Linn. (Family: Sapindaceae)

Sanskrit: Indravalli, karnasphota

English: Balloon Vine

Tamil: Moddakattan

Cardiospermum halicacabum is a slender climber found growing throughout India up to 1,200 m elevation. The tender shoots are used as a vegetable, whereas the whole plant is used for medicinal purposes. The plants belong to the group of ten auspicious herbs or *dasapushpa* (dasa: ten; pushpa: flowers), which are supposed to promote health and remove unhealthy tendencies, including the urge to commit sinful acts.³⁰ The drug appears in later Ayurvedic texts. The herb is used for rheumatism, nervous disorders, sprains, lumbago, edema, and earache. The leaves are used for wound healing, in piles, for treatment of asthma, and to relieve fever associated with cough.^{30,31} The herb is very commonly used in food in Tamil Nadu to get relief from rheumatic complaints, probably because of its use in Siddha medicine. It is also used in skin disorders to treat eczema and herpes.³²

There are two varieties of *Cardiospermum halicacabum* with differences in the size and shape of the fruit, and in the size and shape of the leaves; the fruits of *Cardiospermum halicacabum* var. *microcarpum* have smaller, winged sharply three-lobed fruits, and smaller leaves, whereas *Cardiospermum halicacabum* var. *luridum* has larger bloated three-lobed fruits, which are not winged, and larger leaves.³³ It is not certain which of these varieties has been used in the various investigations, and the impact of this on the results obtained; both varieties are probably similar in activity and used interchangeably; however, this needs to be verified. The results are cited as in literature. It is likely that the investigations from India used the more widespread var. *microcarpum*; there is also the fact that *Cardiospermum halicacabum* var. *luridum* was earlier identified as *Cardiospermum canescens* in India. Investigations from Germany probably used the var. *luridum* from the picture of the plant published along with the review article summarizing German investigations.³⁴

A large number of constituents have been isolated from the aerial parts—flavonoids (apigenin, luteolin, kaempferol-3-rhamnoside and quercetin-3-rhamnoside), several pentacyclic triterpenoids, hydrolysable tannins, sterols (campesterol, β -sitosterol, stigmasterol, β -amyrin), and quebrachitol.³⁴

The anti-inflammatory activity has been studied in several experimental models—granuloma pouch,³⁵ cotton pellet implantation,^{35,36} carrageenan-induced paw edema,³⁶ and in vitro studies.³⁷ The topical anti-inflammatory activity of a 95-percent ethanolic extract has also been studied in mice and the heptane fraction of this extract at 232 μ g per ear was found to exhibit potent activity, probably through inhibition of the enzyme phospholipase A2.³⁸

Studies conducted using an alcoholic extract of the fresh flowering plant of *Cardiospermum halicacabum* in the form of a cream has been included here since it is used in the form of a homeopathic mother tincture, and hence is comparable to that used in herbal medicine.

Neurodermatitis, atopic dermatitis, and eczema

Neurodermatitis is an itchy, eczema-like skin condition caused by repeated scratching, whereas atopic dermatitis is inflammation of the skin caused by allergy. In an open observational study, 512 patients with neurodermatitis were treated with *Cardiospermum* cream; 42 patients served as control and used both the base cream without the active drug and the *Cardiospermum* cream. It was found that there was reduction in the erythema when using the active cream as judged by reduction in redness. In addition, patients could reduce their other medications—corticosteroids and antihistamines.³⁹ In another open observational study, similar results were obtained from patients with eczema.⁴⁰ In another controlled double-blind study in patients with atopic dermatitis, the superior efficacy of the *Cardiospermum* cream against the base cream⁴¹ and of comparable efficacy to bufexamac has been observed.⁴² These results have led to the cream being allowed to be used in Germany in 1995 for inflammatory skin disorders accompanied by itching, such as eczema and neurodermatitis.³⁴

Aerial parts of *Cardiospermum halicacabum* var. *microcarpum* are sold as fresh herbs in the market in Chennai (earlier Madras) especially after the rains. The leaves are often eaten both raw and cooked as food in Chennai to relieve joint pain. The LD₅₀ of the alcoholic extract when injected intraperitoneally in mice is 20 mg·25 g⁻¹ body weight.³⁵ In the open study, the tolerability of the *Cardiospermum* cream was evaluated as good to very good by 82 percent of the patients.³⁹ The *Cardiospermum halicacabum* ointment was well tolerated, and in efficacy distinctly superior to the ointment base in a double-blind study.⁴¹ The tolerability of the bases used for the ointment and the tincture of *Cardiospermum halicacabum* did not show any irritation or allergic reaction.³⁴

***Pongamia pinnata* Pierre (Family: Fabaceae)**

Latin syn: *Pongamia glabra* Vent.

Hindi: Karanj

Sanskrit: Karanj

Tamil: Poongam

English: Indian Beech, Pongam
oil tree

Pongamia pinnata is a medium-sized tree with shiny leaves found almost throughout India up to an elevation of 1,200 m. All plant parts are used medicinally and the plant is a reputed drug for skin problems. The leaves, seed, and bark are considered to be useful in skin problems because of their anti-inflammatory, analgesic, and antiseptic properties.⁴³ The seed paste and seed oil especially are highly regarded for the treatment of scabies, herpes, leukoderma, and other skin diseases.⁴⁴

The tree has been extensively investigated for its chemical constituents and a large number of different classes of compounds have been isolated—flavones, flavone glycosides, furanoflavones, and chromenoflavones, sterols, triterpenes, phenylpropanoid compounds, fatty acids, aminoacids, etc. The seeds contain furanoflavones—karanjin, pongapin, kanjone, and pongaglabrone, the diketone—pongamol. The oil has been clinically shown to be nonirritating. Karanjin, one of the major flavones of the seeds, is said to be the

active principle, which is responsible for the curative effect of the oil in skin diseases.⁴⁴

The few studies carried out so far support the use of *Pongamia pinnata* in skin problems. Thus *Pongamia pinnata* seed extracts at 50 mg·kg⁻¹ to 100 mg·kg⁻¹ given intraperitoneally showed anti-inflammatory, analgesic, and antiulcerogenic effect in rats.^{45,46} It has been suggested that the anti-inflammatory effect may be owing to the modulation of eicosanoid formation in inflammation.⁴⁵ In addition, the seed oil has been shown to possess antibacterial activity against 14 strains of pathogenic bacteria mainly because of inhibition of cell membrane synthesis in the bacteria.⁴⁷ In vitro experiments have shown that the aqueous seed extract inhibits growth of the herpes - virus—HSV-1 at 1 mg·ml⁻¹ and HSV-2 at 20 mg·ml⁻¹—in Vero cells.⁴⁸

The only clinical evidence comes from a study that has been published as an abstract.⁴⁹ Thus, in an open, exploratory study, patients with a wide variety of skin complaints—herpetic lesions due to *Shingles zoster* (infection of the nerves characterized by painful rash) and *Herpes genitalis* (painful blisters caused by the herpes simplex virus 2 producing soreness, itching, and painful blisters in the genital area), impetigo (blisters around the mouth due to skin infection caused by bacteria, especially *Staphylococci*), ringworm, *Pityriasis versicolor* (a skin problem caused by fungus and characterized by white, brown, or colored flaking skin on the neck and trunk), and eczema were treated with *Pongamia* seed oil, a 1:1 sterile aqueous extract of *Pongamia* seed, or *Pongamia* root. The control group received only paraffin oil for application. “Remarkable” healing effects were seen with *Pongamia* seed oil for herpetic lesions due to *Shingle zoster* and *Herpes genitalis*, whereas the seed extract helped in treating *Shingles zoster*. Impetigo was helped by both the oil and seed extract, whereas oil, seed extract, and root extract were all active in the case of ringworm. There is no mention of its effect on eczema and *Pityriasis versicolor*.

Further clinical studies are warranted since the preliminary results are promising. Although a lot of work has been done on the chemical constituents of the seed oil, it would be useful to establish the composition of the material being used for the trials. This would be important since it has been mentioned in earlier work, that seed⁵⁰ and seed

oil⁵¹ are toxic. However, seeds were nontoxic after solvent extraction⁵¹ and the purified oil is safe for use.⁵² Safety studies have been carried out on the seed aqueous extract.⁵³

NOTES

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LEUKODERMA/FOLLICULAR ECZEMA

Leukoderma is a skin condition caused by the inability of melanoblasts to synthesize melanin. White patches appear on the skin wherever melanin is lost. Many plants have been described for its treatment in Ayurveda. The incidence of the disease is estimated to be 3 percent higher in India than the world incidence of 1 percent.¹

***Psoralea corylifolia* Linn. (Family: *Fabaceae*)**

Sanskrit: Bakuchi	Tamil: Karporgam
Hindi: Bavchi	English: Scurfy pea

Psoralea corylifolia is an erect annual herb with bluish purple flowers found growing wild throughout India. The seeds are a reputed drug for the skin in Ayurveda, especially for leprosy, leukoderma, and psoriasis, and also for inflammatory skin disorders, both in the form of topical application as well as oral administration.²

The seeds have been extensively investigated for their chemical constituents. They contain 0.05 percent essential oil, 10 percent of a brown fixed oil, a nonvolatile oil containing terpenoids, approximately 9 percent resin, furanocoumarins—psoralen, isopsoralen identical with angelicin, coumesterol derivatives—psoralidin and isopsoralidin, flavonoids—bavachalkone, bavachinin, isobavachalkone, bavachin, and isobavachin—a monoterpenoid phenol bakuchiol, chalcones, isoflavones—corylin, neobavaisoflavone, corylinal, psoralenal—triacontane, sitosterol, and stigmasterol.^{2,3}

Psoralen and isopsoralen are considered to be the active principles useful in leukoderma of nonsyphilitic origin.² Psoralen has been shown to stimulate melanin production by accumulation in the melanocytes and photooxidation of the dihydroxyphenylalanine present there to melanin.⁴⁻⁶ The aqueous⁷ and alcoholic^{7,8} extracts of *Psoralea corylifolia* seeds have shown inhibitory activity against *Staphylococcus aureus*. The petroleum ether extract of the seeds inhibited the growth of *Staphylococci* at a concentration of 2-4 $\mu\text{g}\cdot\text{ml}^{-1}$, especially those of *Staphylococcus aureus* that are resistant to several antibiotics such as penicillin, streptomycin, chloramphenicol, erythromycin, and tetracycline.⁹ Later on, an oily compound was isolated that inhibited *Staphylococcus aureus* at 0.5 $\mu\text{g}\cdot\text{ml}^{-1}$ with an activity comparable to that of chloramphenicol.^{10,11} Bakuchiol has been studied for its anti-staphylococcal activity.¹² In addition, the seeds have also been shown to have immunomodulatory activity,¹³ whereas bakuchiol and the flavonoids—*isobavachin* and *isobavachalcone*—have been shown to have potent antioxidant activity.¹⁴ The flavonoid, *bavachinin*, has been shown to exert marked anti-inflammatory, antipyretic, and mild analgesic activity.¹⁵

Leukoderma

The preliminary exploratory studies were carried out with different preparations, derived from the seeds of *Psoralea corylifolia*, applied topically on the affected areas for a variety of skin disorders. From these exploratory studies it was found that the oleoresin of the seeds, which contained most of the essential oil, was most useful in leukoderma patches.¹⁶

The oral clinical use of the powdered seeds of *Psoralea corylifolia* for the treatment of leukoderma is dose dependently attended by severe side effects such as nausea, vomiting headache, and severe purging, so that in all further clinical studies, a mixture of psoralen and isopsoralen was used in doses of 10-30 $\text{mg}\cdot\text{day}^{-1}$ for 4 months with good results. However, the drug can no longer be considered an herbal preparation; the results of such studies have been summarized.³

Follicular eczema

Follicular eczema is an infection of the hair follicle caused by *Staphylococcus aureus*. The seeds of *Psoralea corylifolia*, which have exhibited good antibacterial activity, may be of use in this condition, which is characterized by chronicity. In addition, antibiotics give only temporary relief. The alcoholic extract of the seeds was dissolved in coconut oil and 5-30 ml of the oil was applied twice a day for periods ranging from 2 to 4 weeks in 21 patients. A total of 17 out of the 21 patients had significant relief and when followed up for 2 years there was no relapse. There were four dropouts after 2 weeks. At the end of 2-4 weeks of treatment 12 patients had complete relief, 2 had marked relief, and 3 patients had moderate relief. Continuation of the treatment for a few more days resulted in all patients obtaining complete relief.¹⁷

Topical use of the seed oil can cause irritation, blistering, and also act as a vesicant. The oleoresin extract of the seeds had the official status in the *Indian Pharmacopoeia*, 1960, as “Babchi ointment” or “Application of *Psoralea*.” The strength of the oil or its preparation has to be adjusted to prevent redness beyond that already present in the leukoderma patch.^{2,18}

It appears that the external application is useful in certain cases, but is attended by side effects such as irritation of the skin; therefore, until it is possible to standardize the product it is likely to be of use only in the form of the pure compounds and derivatives and not as a whole drug.

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PSORIASIS

Psoriasis is a skin condition characterized by itching, scaling, and hyperproliferation of skin, and is estimated to be afflicting 1-3 percent of populations. Although a number of plants have been used in Ayurveda for the treatment of psoriasis, only a few of them have been evaluated to some degree. The best known of these are *Aloe vera*, *Azadirachta indica*, *Centella asiatica*, and *Wrightia tinctoria*. In the

case of *Azadirachta indica*, its bitter principle, nimbidin, has been used and is therefore not covered here since nimbidin cannot be considered an herbal drug.

***Aloe vera* Tourn. ex Linn (Family: Liliaceae)**

In a double-blind, placebo-controlled study, the efficacy and tolerability of a 0.5 percent of *Aloe vera* cream was studied on 60 patients with mild-to-moderate psoriasis. Patients had the disease for an average of 8.5 years before entry to the trial. Patients were given either *Aloe vera* cream or placebo and asked to apply the cream thrice a day for 5 consecutive days for a total of 4 weeks. The progress of patients was evaluated every week. By the end of the trial, the *Aloe vera* extract cream had cured 25 out of 30 patients as compared to 2 out of 30 in the placebo group, resulting in considerable clearing of psoriatic plaques. No side effects were observed.¹

***Centella asiatica* (Linn.) Urban (Family: Apiaceae)**

In a small clinical study, seven patients with psoriasis were treated with a cream containing an oil and water extract of *Centella asiatica* (see Plate 8 in color gallery) for periods ranging from 3 to 8 weeks. It was found that five out of seven patients showed complete clearance of the lesions. None of the patients experienced any side effects. One of the patients, who had frequently been using steroids in the past, showed only partial recovery.² Except for one patient, the remaining six patients were routinely asked to apply salicylic acid ointment 12 hours after the application of *Centella*. In vitro studies have shown that *Centella asiatica* extract has a keratinocyte antiproliferant activity.³ Further studies are needed with larger patient numbers.

***Wrightia tinctoria* R. Br. (Family: Apocyanaceae)**

Sanskrit: Sweta kutaja, Madhura
kutaja

Tamil: Vetpalai

Hindi: Indrajau

English: Pala Indigo Plant

Wrightia tinctoria is a small deciduous tree found almost throughout India. The bark is sometimes used to adulterate the bark of *Holarrhena antidysenterica*, which is covered in Chapter 3, "Gastrointestinal agents," for the treatment of amebiasis. The leaves contain indigotin, which yields 0.3-0.5 percent of the dye indigo, known as Mysore Pala Indigo, used for dyeing fabric.⁴ The tree is useful medicinally. The leaves are used in Ayurveda for toothache and hypertension; the bark and seeds for dyspepsia, flatulence, leprosy, psoriasis, and fever.⁵ The leaves are especially useful in skin problems, and in Siddha medicine forms part of many combination drugs used for the treatment of psoriasis.

Indigotin, indirubin, tryptanthrin, isatin, anthranilate, and rutin are the major constituents isolated from *Wrightia tinctoria*.⁶ The leaves also contain β -amyrin, lupeol, β -sitosterol, and ursolic acid.⁷

Coconut oil containing the leaf extract of *Wrightia tinctoria* showed significant analgesic and anti-inflammatory activity.⁸ In mice, *Wrightia tinctoria* in emulsion showed reversal of parakeratosis, which is a feature of psoriasis.⁹

In an open running trial, 281 patients with psoriasis were treated between 1980 and 1987. The trial drug coded "777" oil was obtained by exposing fresh leaves of *Wrightia tinctoria* in coconut oil to sunlight for 3 days, followed by filtering off the oil. Patients were given 5 ml of the oil twice a day and patients were also asked to apply the oil over the affected regions and expose these areas to sunlight for 5-10 minutes.^{10,11} There were 67 dropouts. Of the remaining 214 patients who completed the course of treatment, 108 patients had complete relief, 49 patients had marked relief, 39 had moderate relief, 17 had mild relief, and 1 patient had no relief. Disappearance of scaling was taken as mild relief. Disappearance of scales and erythematous changes were considered as moderate relief, transformation of papular to macular lesions as marked relief, whereas total disappearance of all clinical symptoms was considered as complete relief. A total of 30 patients were taken to undertake a detailed study for biopsy and also followed up for 4 years. There was no recurrence in 50 percent of the cases, although in 30 percent recurrence was postponed to more than 3 years. Recurrence was accompanied by great reduction in in-

tensity, and there was no occurrence of any of the complications such as arthritis and carona psoriatica.¹⁰

Nonspecific dermatitis

In an open trial, 20 patients with histologically confirmed nonspecific dermatitis, who presented extensive skin lesions, burning, and intense itching, were treated with oil of *Wrightia tinctoria* taken orally twice a day, as well as the oil being applied topically, followed by short exposure to sunlight for a period of 6 weeks. Of these, 14 patients showed complete relief and no relapse was observed for more than 3 years.¹⁰

The acute toxicity (72 hours) of 777 oil prepared from *Wrightia tinctoria* leaves was studied in mice and rats and the LD₅₀ was found to be 45 ml·kg⁻¹ in mice and 30 ml·kg⁻¹ in rats. A 30-day subacute toxicity carried out at three dosage levels—1, 5, and 10 ml of the oil extract with controls—was found to be nontoxic. Major organs such as liver, kidney, spleen, heart, and lung showed no toxicity or histopathological changes.¹⁰

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WOUND HEALING PLANTS

Plants have served as healing agents for wounds since time immemorial. The healing of wounds has been dealt with as separate topics in the major Ayurvedic texts of Sushruta, Jivika, and Vagbhata, because of the importance attached to this topic as a matter of immediate concern in those days owing to the living environment, and the frequent battles and wars. The *Sushruta Samhita* has two separate chapters dealing with the treatment of the injuries and the handling of patients, describing the use of more than one hundred plants for the treatment of wounds, both as single drugs and in combination.¹ Sushruta has mentioned not only procedures and drugs to obtain a clean wound (*vrana shodan*) followed by healing (*vrana ropan*) but also medicines to help prevent the formation of keloid scars.²

***Aloe barbadensis* Mill. (Family: *Liliaceae*)**

Latin: <i>Aloe vera</i> Tourn. ex Linn.	Hindi: Ghi-kuvar
Sanskrit: Ghrita kumari, kumari	Tamil: Kattalai
English: Barbados Aloe, Indian Aloe	

Aloe barabadensis is a perennial plant with succulent leaves originally introduced from Africa into India, now found in a semiwild

state in many parts of the country. The leaves are widely used in Ayurvedic medicine. Its usage varies corresponding to the part of the leaf being used—the outer thick covering of the leaf, in which the steamed leaf without pulp is applied to abscesses; the inner yellow juice or exudate, which flows out from the leaf after cutting, darkens and solidifies after a while to a dark mass called aloes containing anthraquinones, is a drastic purgative; and the inner mucilaginous leaf pulp or gel, composed mainly of carbohydrates, is considered a tonic for the liver, in female complaints such as amenorrhea and dysmenorrhea, and during menopause, good for the eyes, and for the treatment of burns, wounds, and skin diseases.^{3,4}

Aloe barbadensis gel contains about 98.5 percent of water with polysaccharides as the major constituents—pectins, hemicelluloses, glucomannan, acemannan, the major carbohydrate component and mannose derivatives where mannose-6-phosphate is the major sugar component. Also present are amino acids; lipids; sterols such as campesterol, lupeol, and β -sitosterol; tannins; and enzymes.⁵ In addition, glycoproteins with wound healing activity⁶ and aloeride, a potent immunostimulatory polysaccharide component,⁷ have been isolated.

The topical^{8,9} and oral⁸ wound healing activity of *Aloe vera* has been extensively studied. Studies on the healing of dermal wounds observed that there were increased levels of collagen in the granulation tissue¹⁰ and improved synthesis of glycosaminoglycan component¹¹ of the extracellular matrix in a healing wound, thereby contributing to improved wound healing. *Aloe vera* also improved healing of full thickness wounds in diabetic rats, where both healing and anti-inflammatory processes are retarded because of diabetes.¹² In addition, *Aloe vera* helped faster healing of burn wounds in guinea pigs by exhibiting an antibacterial effect,¹³ and in rats by its anti-inflammatory and aiding the wound healing activity.¹⁴ The inflammatory process was inhibited by reduction of leukocyte adhesion and of inflammation-causing cytokines.¹⁵ *Aloe vera* was also found to reverse retardation of wound healing caused by silver sulfadiazine¹⁶ and steroids.¹⁷ Other useful activities of *Aloe vera* gel, when applied externally, include a beneficial effect on skin regeneration¹⁸ and its antioxidant activity.¹⁹ The antioxidant activity is dependent on the age of the plant—3-year old plants showing greater antioxidant activity than butylated

hydroxy toluene (BHT), α -tocopherol—2- and 4-year old plants, and also higher levels of polysaccharides and flavonoids.¹⁹

Among the constituents contributing to the observed activity, two immunomodulatory compounds were isolated from the gel of *Aloe vera*.²⁰ Subsequently, acemannan has been shown to accelerate wound healing.²¹ Mannose-6-phosphate, a major sugar in *Aloe vera* gel, improved wound healing in mice over saline controls.²² A glycoprotein fraction has been shown to improve wound healing via cell proliferation and migration.⁶ In addition, an active glycoprotein fraction has been shown to exhibit radical scavenging effect apart from inhibition of cyclooxygenase-2 and thromboxane A₂ synthase inhibition in vitro.²³ Aloeride, a new potent immunostimulatory polysaccharide present up to 0.015 percent of the dry weight of aloe juice, has been isolated.⁷ Thus, many components of *Aloe* gel have been shown to play a useful role in wound healing.

The therapeutic effects of *Aloe vera* were examined in a number of indications in dermal ischemia due to burns, frostbite, electrical injury, distal dying flap, and intra-arterial drug abuse. In burn patients and those suffering from frostbite, patients healed without tissue loss. Tissue necrosis was reversed in intra-arterial drug-abuse patients. The results suggest that *Aloe* acts by inhibition of thromboxane A₂ production and by maintenance of homeostasis both in the wound and also in the surrounding tissue.²⁴

In a placebo-controlled study involving 27 patients with partial thickness burns were treated with *Aloe vera* gel. Patients treated with *Aloe vera* gel showed faster recovery in 11.8 days as compared to those treated with petroleum jelly gauze (18.2 days), which was considered statistically significant.²⁵

In a randomized double-blind study, 100 patients with 10-40 percent burns had wounds dressed either with *Aloe vera* extract or routine dressing done every 3 days. The main wound healing time was significantly lower ($p < 0.001$) in the case of those treated with *Aloe vera* as was bacteriological control ($p < 0.012$).²⁶

There are a number of factors involved in the use of *Aloe vera* gel. The gel itself is preferably used fresh due to possible decomposition⁵ and also the probable negative effect on the clinical outcome of added stabilizers²⁷ and the further processing that the gel undergoes.²⁸ Ex-

perimental studies have shown that *Aloe vera* gel may delay wound healing in the later stages.²⁹ In first- and second-degree burns in mice, *Aloe vera* gel increased the rate of healing, improved epithelialization, and reduced inflammation, but proved to be not very effective for third-degree burns.³⁰ As information becomes available on the contribution of the various components of the gel and the time of application to wound healing, it should be possible to obtain more consistent results, since negative trials have also been reported with *Aloe* gel. More clinical trials are required to further validate the use of *Aloe vera* gel. The topical use of the gel is generally considered safe. Cases of irritation may be attributed to the presence of traces of anthraquinones. However, the possibility of allergic reactions needs to be borne in mind.⁵

***Centella asiatica* (Linn.) Urban (Family: Apiaceae)**

The use of *Centella asiatica* (see Plate 8 in color gallery) in chronic venous insufficiency has been covered in Chapter 6, “Cardiovascular drugs,” and its use as a mental rejuvenator in Chapter 12. *Centella asiatica* is well known in Ayurveda^{31,32} as a local stimulant of the skin, and is used therefore in skin diseases, such as herpes, eczema, and psoriasis and in wound healing.

Extracts of *Centella asiatica* have been evaluated in experimental animals. Thus both alcoholic³³ and aqueous extract³⁴ of *Centella asiatica* when applied to open wounds in rats showed an increased cell proliferation and protein synthesis. Treated wounds healed faster as compared to untreated controls showing faster epithelialization and rate of wound contraction^{33,34} in experimental wounds. The extract as well as the total triterpenes—asiaticoside, asiatic acid, and madecassic acid reconstituted from the plant in the ratio 4:3:3 have been shown to increase the percentage of collagen in human skin fibroblast cultures³⁵ and also to stimulate glycosaminoglycan synthesis in experimental wounds in rats.³⁶ These three triterpenes have been shown to hasten wound healing by increasing human collagen I synthesis.³⁷ In addition, it was shown that the presence of the glucose moiety was not necessary for collagen synthesis.³⁷ Asiaticoside improved wound healing in both normal and delayed healing models

owing to increased collagen synthesis and angiogenesis,³⁸ and was also shown to enhance induction of antioxidant levels at initial levels of healing in excision type cutaneous wounds in rats.³⁹

In a study with 27 patients with slow healing wounds of varied etiology, patients were treated topically with an ointment containing 1 percent *Centella asiatica* extract or with a 2 percent powder in addition to three intramuscular injections of asiaticoside per week. Accelerated healing of wounds was seen in 55 percent of patients, with improvement in 15 percent. The remaining 30 percent of patients showed no perceptible effect of treatment.⁴⁰ In another study, 64 percent healing was observed when a preparation in which asiaticoside was the major ingredient was used in patients with intractable and soiled wounds.⁴¹ In another open study, a formulation containing 89.5 percent of *Centella asiatica* produced healing in 64 percent patients, whereas 16 percent showed improvement in wounds.⁴² In second- and third-degree burns, topical application of a preparation of *Centella asiatica* hastened healing, averted infection, and prevented the formation of hypertrophic scars.⁴³

In some individuals, hypersensitivity reactions can occur when *Centella asiatica* is applied topically;⁴⁴ however, it has been suggested that this could be due to other ingredients.⁴⁵

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OTHER WOUND HEALING PLANTS

***Azadirachta indica* A Juss. (Family: *Meliaceae*)**

Azadirachta indica is among other plants that have been investigated for burn wounds. The tolerability of a preparation of *Azadirachta indica* was studied in seven patients with second-degree burns and was found to be good, with an initial stinging, which passed off on continued application, and no other adverse effects reported. Healing took place in 4 weeks with burns epithelialized and scars being soft, supple, and well pigmented. A randomized comparative trial was then conducted with 17 patients who received either *Azadirachta* cream or silver sulfadiazine. Ulcer scores at the end of 2 weeks were found significantly less in the *neem* group; epithelialization was better at 88.89 percent in the *neem* group as compared to 62.5 percent in the silver sulfadiazine group. In addition, in the *neem* group, the healing of cartilaginous areas was without deformity. Only in the silver sulfadiazine group were complications such as sepsis, contractures, and hypertrophy of scars noticed, leading the authors to conclude that *neem* appeared to be a safe and effective prohealer.¹

NOTE

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FRACTURE HEALING PLANTS

The subject of fractures, their etiology, pathology, specific signs and symptoms, treatment, and possible complications have been dealt with in detail in the *Sushruta Samhita* dated 600 BC.^{1,2} In fact, there are certain families that specialize in the setting of bones and their treatment using herbs in South India. Several plants have been used in India for hastening the healing of fractures and for strengthening the bones. Of these *Cissus quadrangularis* has been studied scientifically. There is increased interest in such plants, not only for help in bone healing when injured but also because of their possible use in osteoporosis.

***Cissus quadrangularis* Linn. (Family: Vitaceae)**

Latin: *Vitis quadrangularis* Wall

Hindi: Hadjod

Sanskrit: Asthisamharaka,
Vajravalli

Tamil: Perandai

English: Bonesetter, The edible-
stemmed vine

Cissus quadrangularis (see Plate 10 in color gallery) is a slender perennial climber with quadrangular stems, found leafless when old, growing throughout the hotter parts of India. The leaves and stems are commonly used as a vegetable in South India: as a paste with lentils known as chutney; or sometimes the stem juice is added to dried preparations such as *papad* that are later fried and eaten. The stem is considered to improve digestion and to be useful in piles, and is used widely in healing of fractures. The stems are administered orally and also applied topically to help heal fractures in dislocation and traumatic injury.^{2,3} The Sanskrit, Hindi, and English names refer to this bone-knitting property of the plant.

The plant contains unsymmetric tetracyclic triterpenes apart from δ -amyrin and δ -amyrene in the hexane extract. In addition, several alicyclic lipid constituents have been isolated. From the methanol fraction 3, 3', 4, 4'-tetrahydroxybiphenyl was also isolated.⁴ The

plant also contains calcium oxalate, vitamin C (398 mg per 100g fresh, tender stem), and β -carotene.⁵

Experimental studies using S^{35} were carried out to study the normal healing pattern of fracture in rats.⁶ Weekly intramuscular injection of the alcoholic extract of *Cissus quadrangularis* (0.5 ml equivalent to 0.5 g of fresh drug) was found to accelerate fracture healing in small animals.^{7,8} Histochemical and biochemical studies showed a beneficial effect of the herb.⁹ Isotopic studies using S^{35} , P^{32} , and Sr^{85} showed that systemic use of the herb reduced healing time^{7,8,10} by one-third.¹² Topical application of a paste of *Cissus quadrangularis* increased the healing rate of treated animals by 10-14 days.¹¹ The total extract has a definite influence on both the organic and mineral phase of fracture healing in experimental animals. Ca^{45} uptake studies showed that there was earlier calcification and remodeling owing to the drug. In addition, there was a 90 percent increase in tensile strength in treated animals as compared to 60 percent in untreated controls.¹² Intramuscular administration of the drug showed a stimulatory effect neutralizing the effect on cortisone-treated fractures.¹³ In ovariectomized rats, feeding for 3 months with 500-750 mg·kg⁻¹ of an ethanolic extract of *Cissus quadrangularis* showed significant increase in biomechanical strength comparable to raloxifene, a selective estrogen receptor modulator currently used to treat osteoporosis.¹⁴

In an open trial with controls, 78 patients were enrolled of which in 60 patients a paste of *Cissus quadrangularis* was applied after the fractured fragments were reduced, and the bone was immobilized in the usual fashion with a cast. Of the patients who served as controls, 18 were reduced and immobilized with a cast with no additional treatment. Patients were monitored every week and also checked using X-ray. The patients were assessed based on callus formation, improvement in the clinical picture, time of immobilization, and time required to return to normalcy. Patients using *Cissus quadrangularis* were found to experience some degree of itching, which has been attributed variously to the content of carnosine² and calcium oxalate.⁵ Decreased swelling, greater freedom of movement; smaller callus formation, and 30-40 percent reduction in period of immobilization were some of the benefits of treatment with *Cissus quadrangularis*.^{2,15,16}

In clinical practice in patients of jaw-bone fractures, it was found that addition of *Ocimum sanctum* and *Cissus quadrangularis* along with the usual management of such fractures was found to reduce significantly the time of immobilization.¹⁷

Cissus quadrangularis is often used in food in South India to aid digestion. It is usually well tolerated in the usual doses.¹⁸ When the paste of the plant is applied topically, patients were found to experience some degree of itching, due to the content of carnosine² and calcium oxalate⁵ that subsided without any treatment in a few days. This itching sensation can also occur when taken orally because of the calcium oxalate content. In experiments with *Salmonella typhimurium* tester strains *Cissus quadrangularis* was found to be mutagenic,¹⁹ although the relevance of such experiments for human beings is not clear.

NOTES

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Chapter 10

Gynecological Agents

Plants have been extensively used in Ayurveda to maintain the health of the female reproductive organs. These have been used mostly as combination drugs, and single plants have not been the subject of much scientific investigation. Much of the scientific interest has been directed toward control of fertility, which is not covered in this book. The herbs often used for the treatment of common problems of women are *Asparagus racemosus*, *Boerhaavia diffusa*, *Glycyrrhiza glabra*, *Saraca asoca*, *Symplocos racemosa*, *Withania somnifera*, *Mesua ferrea*, and others.

GALACTAGOGUE

Lactation is initiated by an increase in levels of prolactin, a hormone produced by the pituitary glands. A number of plants have been used in Ayurveda to stimulate milk production, in case of lactational inadequacy, both taken internally and also applied externally. However, there is a dearth of scientific information on such plants.

Asparagus racemosus Willd.
(Family: *Liliaceae*, *Asparagaceae*)

The use of roots of *Asparagus racemosus* for the treatment of duodenal ulcers has been covered in Chapter 3. The roots are used in Ayurveda for stimulating milk flow and protecting pregnant women against threatened abortion. In postpartum and estrogen-primed rats intramuscular injection of the alcoholic extract of the roots was

shown to exert a lactogenic effect, increasing milk yield, and breast lobular-alveolar tissue, which has been attributed to an increase of prolactin levels or to a release of corticosteroids.¹ A galactagogue action was also seen in buffaloes² and goats.³ The saponin fraction, especially shatavarin I, has been shown to have an antioxytotic action on uterine tissue and an anti-ADH^{4,5} activity supporting its use in threatened abortions. In an open exploratory study, 15 women with deficient milk during lactation were given 2 tablets of a preparation containing *Asparagus racemosus* twice a day after meals. The trial drug contained 40 mg *Asparagus racemosus* extract, 10 mg processed iron pyrites, and 400 mg dicalcium phosphate. Out of the 15 women, 11 reported an increase in milk yield together with improved appetite. Four patients independently tried stopping the intake of the drug and the milk yield was found to decrease, which improved once again with the resumption of the intake of the drug.⁶

In a randomized controlled trial of *Asparagus racemosus*, increase in milk yield was not found different from placebo.⁷ The preparation contained other herbs although *Asparagus racemosus* was the major herb in the trial preparation. The results are not necessarily attributable to *Asparagus racemosus* because of the addition of other herbs. The trial preparation also led to a decrease in prolactin levels. However, considering the reputation of *Asparagus racemosus* in increasing milk yield, studies to clarify possible reasons for this lack of response are required, preferably after standardization of the product.

NOTES

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ANTILEUKORRHEAL PLANTS

Leukorrhea or the white discharge from the vagina is commonly seen in women and termed *sweta pradara* in Sanskrit (*sweta*: white; *pradara*: discharge or flow). Clinical trial data with single herbs is scanty. A single herb for which an exploratory trial was conducted is *Boerhaavia repanda*.

Boerhaavia repanda Willd. (Family: Nyctaginaceae)

Boerhaavia repanda is a straggly herb found growing throughout India. The leaves and tender shoots are used as a vegetable. The root has anthelmintic activity and the root powder showed a significant therapeutic effect in the treatment of leukorrhea.¹ Fresh roots of *Boerhaavia repanda* were collected, shade-dried, powdered, and used in doses of 500 mg.

In an open clinical study, 32 patients in the age group of 20-38 years with leukorrhea were asked to take 500 mg (1 tablespoon) of *Boerhaavia repanda* root powder twice a day for 30 days. All patients reported marked improvement within a few days of treatment; white discharge stopped after 15 days but patients were asked to continue treatment for a further 2 weeks. No side effects were noticed, except for a little nausea.²

In an open study with controls, 20 female patients aged between 20 and 38 years with leukorrhea were asked to take 500 mg of the powder twice a day with milk or water for 15 days. A control group of 5 patients were maintained as control. At the end of the treatment period all 20 patients were found cured.³

NOTES

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ANTIMENORRHAGIAL PLANTS

Excessive loss of blood during menstruation is termed menorrhagia. It has been suggested as due to hormonal imbalance in estrogen and progesterone. Bleeding between periods is termed metrorrhagia. Excessive bleeding is termed *raktapradara* (rakta: blood; *pradara*: flow) in Ayurveda. A number of plants, especially those containing tannins, have been used to control menorrhagia; however, very few plants have been subjected to clinical trials especially as a single drug.

***Saraca asoca* (Roxb.) de Wilde (Family: Caesalpinaceae)**

Sanskrit: Ashoka

Hindi: Asok

Tamil: Asogam

Saraca asoca is a small evergreen tree found almost everywhere in India. The stem bark is extensively used in Ayurveda for the treatment of menorrhagia especially due to uterine fibroids, uterine disorders, and leukorrhea, and to treat depression in women.¹ The bark is used in numerous multiplant preparations in the market. It has, however, been little investigated as a single drug. The bark has numerous polyphenolic compounds—procyanidin B2, leucopelargonidin, leucopelargonidin-3-O-β-D-glucoside, leucocyanidin, (-)-epicatechin, (+)-catechin, flavonoids, and sterols.¹ Experimental studies have shown that the bark has oxytocic activity in rats, guinea pigs, and isolated human uterine preparations. The uterine response to the extract was dependent on

hormonal environment and the state of gestation. Estrogen-primed rats were more sensitive to the alcoholic extract.² A pure phenolic glycoside (P₂) showed in vitro and in vivo oxytocic activity at very low concentrations on uteri of several species.^{3,4}

Considering the importance of the drug in Ayurveda it has been clinically little investigated as a single drug. Only one small trial with 10 patients has been reported in which the drug was given parentally. Commercially available "Injection *Ashoka*" 2 ml of was given intramuscularly in 10 cases of metromenorrhagia. All patients responded to the treatment with good results and menstrual flow was normalized.⁵ Much more work is required experimentally to determine the mode of action in addition to holding clinical trials using the oral route.

***Mimosa pudica* Linn. (Family: *Mimosaceae*)**

Sanskrit: Lajjalu	Tamil: Thottalsulungi
Hindi: Lajwanti	English: Sensitive plant

Mimosa pudica is a common weed found throughout the warmer parts of India. The roots contain tannin (10 percent), mimosine, and calcium oxalate. In an exploratory clinical study in patients with dysfunctional uterine bleeding, the aqueous extract of the root was given in a dose of two to three 500 mg capsules thrice a day. The period of treatment was variable from a few months to 4 years. The response was considered promising enough to warrant further studies.⁶

NOTES

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Chapter 11

Antidiabetic Agents

With over 100 million people affected worldwide, diabetes mellitus is the most common, chronic endocrine disorder of carbohydrate, fat, and protein metabolism. Characteristics of the disease are symptoms such as excessive thirst, hunger, weight loss, fatigue, blurred vision, etc. Diabetes has been described in Ayurveda in both the *Caraka* and *Sushruta Samhitas* under the name *madhumeha* (*madhu*: honey; *meha*: urine) or *prameha* meaning excessive urine (*pra*: excessive).

There is also a remarkable correspondence between the descriptions of the etiology and management of the disease in Ayurvedic texts and its allopathic correlates. The two types of diabetes described today are insulin-dependent diabetes mellitus (IDDM), because of nonfunctional or damaged beta cells in the pancreas, and noninsulin-dependent diabetes mellitus (NIDDM). A similar classification exists in Ayurveda with *sahaja prameha* caused due to congenital reasons and *apathyaanimitaja prameha* considered to occur due to unsuitable choice of food or consuming excessive food.¹

A large number of plants have been used in Ayurveda for the management of diabetes mellitus, and 148 plants of 50 families have been reviewed. As, elsewhere in Ayurveda, combination drugs are the preferred mode of therapy. Some 40 plants have been used that have been reviewed by several authors.²⁻⁴

Scientific work has focused on phytochemical examination, and in experimentally demonstrating hypoglycemic activity in small animals made diabetic by alloxan, streptozotocin, and sometimes by adrenaline. Therefore, most studies have concentrated on the control of hyperglycemia.

Only a few studies have been carried out to evaluate the effect of the drugs on complications of diabetes mellitus, such as nephropathy, neuropathy, and retinopathy, which need to be addressed especially since synthetic oral hypoglycemic agents and insulin, which form the mainstay of treatment of diabetes by controlling hyperglycemia, nonetheless have serious side effects and fail to alter the course of diabetic complications. *Eugenia jambolana* and *Momordica charantia* have been shown to yield good results in the amelioration of diabetic complications such as diabetic nephropathy,⁵ fructose-induced insulin resistance,⁶ and cataract⁷ in experimental animals. The two plants also partially prevented diabetic neuropathy⁸ in small animals. There are conflicting reports on the hypoglycemic activity of some plants that may be attributed to a number of factors such as botanical identity of the drugs, time and place of collection, method of preparation, mode of administration, and type of experimental animal used.²

Clinical data is generally of preliminary nature. There are roughly seven single plants, which have been studied in some detail, and these are covered here. Work on other potentially useful single drugs for which exploratory clinical work is available is presented in brief. Also discussed are a few plants used clinically to treat diabetic complications.

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MAIN PLANTS

***Azadirachta indica* A Juss. (Family: Meliaceae)**

Latin: <i>Melia azadirachta</i> Linn.	Hindi: Neem, Nimb
Sanskrit: Nimba	Tamil: Veppan, Vembu
English: Margosa	

Azadirachta indica or the *neem* is a large evergreen tree found growing throughout India. It is also cultivated widely. The *neem* tree has been used since antiquity in India for a variety of ailments. Since the tree is found growing everywhere, it often serves to provide twigs that are used as chewing sticks for cleaning the teeth and gums; leaves that are used for skin problems and during infections such as measles, chicken pox, etc. to help soothe itch. In addition, young leaves are plucked and chewed as a medicine to control blood sugar and to improve immunity. Flowers of the *neem* tree serve to control blood pressure and the seed kernel serves as an antifeedant for controlling insect attack. Leaves, seed oil, and bark of the tree have been used to treat diabetes. Traditionally, *neem* has been used for the treatment of skin diseases, fevers including malaria and rheumatism and other inflammations.¹ Every part of the *neem* tree is thus used for numerous indications.

A very large number of substances have been isolated from different parts of the *neem* tree. These have been terpenoids—diterpenoids, tetranortriterpenoids (liminoids), and triterpenoids—steroids, coumarins, fatty acids, flavonoids, fatty acid derivatives, hydrocarbons, and sulfur compounds.^{1,2}

The aqueous leaf extract has been shown to produce hypoglycemia in small animals when administered orally at $200 \text{ mg}\cdot\text{kg}^{-1}$ (10 percent $\text{w}\cdot\text{v}^{-1}$ aqueous leaf extract)³ and at $0.15 \text{ ml}\cdot\text{kg}^{-1}$ (50 percent $\text{w}\cdot\text{v}^{-1}$ aqueous leaf extract) when administered intravenously⁴ to dogs. However, in another study, oral aqueous leaf extract, prepared by decocting the leaf, seed oil, and the compound nimbidin, was tested at dose levels of 1, 5, and $10 \text{ ml}\cdot\text{kg}^{-1}$ body weight and it failed to reduce blood glucose levels, whereas seed oil at $2.5 \text{ ml}\cdot\text{kg}^{-1}$ and nimbidin at $200 \text{ mg}\cdot\text{kg}^{-1}$ body weight were active and exhibited significant hypoglycemic effect in both normoglycemic-fasted rabbits and glucose-fed animals in glucose tolerance test.⁵

Aqueous fraction of alcoholic^{6,7} and methanolic extracts⁸ of *neem* leaves exhibited hypoglycemic and antihyperglycemic effect in adrenaline-induced, glucose-fed,⁶ and streptozotocin diabetic rats.^{7,8} Fractions exhibiting hypoglycemic activity were found to be rich in flavonoid glycosides.⁷ An evaluation of the leaves of four Ayurvedic medicinal plants—*Azadirachta indica*, *Gymnema sylvestre*, *Catharanthus roseus*, and *Ocimum sanctum*—in normal and streptozotocin-diabetic rats for blood sugar lowering activity showed that *A. indica* leaf had the most potent blood sugar-lowering activity and the best safety margin.⁹

In addition, *neem* leaf extract or seed oil exert their hypoglycemic effect in rabbits both when given as pretreatment before alloxan or after induction of diabetes suggesting that *neem* could be useful for control of blood sugar in diabetes, and also for helping to retard or to prevent onset of the disease.¹⁰ *Neem* oil has been shown to reduce blood glucose levels in several experimental models in rabbits,¹¹ and in both normal and alloxan-diabetic rats.¹²

A series of studies have been carried out to elucidate the mechanism of action. It has been suggested that *neem* extract is an effective hypoglycemic agent only in animals having residual and healthy beta cells and it can act only in the presence of a stimulus, such as an external glucose load. *Neem* increases peripheral glucose utilization by blocking the effect of epinephrine on glucose metabolism.¹³ However, in an in vitro experiment *neem* extract did not enhance glucose uptake or glycogen synthesis in isolated rat hemidiaphragm.¹⁴ *Neem*

leaf extract also blocks in a significant fashion the serotonin inhibition of insulin secretion mediated by glucose.¹⁵

In an exploratory clinical trial, 5 g of fresh tender *A. indica* leaf paste or an equivalent amount of dried leaf powder filled in capsules given to type I diabetics enabled five out of seven patients to reduce their insulin dosage by 30-50 percent, while maintaining their blood glucose values.¹⁶

In an open uncontrolled study on 85 patients of type II diabetes, who were on conventional allopathic drugs, 5-10 drops per day of *neem* seed oil in soft gelatin capsules was given in two divided doses along with the prescribed treatment. *Neem* oil was found to act in a synergistic manner to conventional drugs, and it was possible to reduce the dosage of other oral antidiabetic drugs and insulin, based on the response of the blood glucose levels of patients to treatment.¹⁷

In an open preliminary study, patients with secondary diabetes were given varying doses of *neem* oil depending upon severity of diabetes: those with mild diabetes received 5 drops, those with moderate diabetes received 10 drops, and those with severe diabetes receiving 15 drops of *neem* oil twice a day. Patients experienced relief in symptoms such as itching, dyspepsia, fatigue, and muscular pain. In addition, patients had improved wound healing. The oil was evaluated as useful in mild and moderate diabetes, and was found to have 50 percent effect on patients with severe diabetes.¹⁸

Considering the preliminary but promising nature of results, further work is required in studying the material being used in the clinical trials and in using larger patient numbers for evaluation. Also to be evaluated is the safety of the preparations.

The use of tender *neem* leaves for health and in diabetes is recommended in traditional medicine, not only in the geriatric population, but also in the pediatric age group of infants. After a review of literature, including various toxicity studies, the leaf, bark extract, and isolated limonoids were considered to have a wide margin of safety.¹ In another review of literature, the leaf extract had experimental LD₅₀ values ranging from 10 to 13 g·kg⁻¹ bodyweight.¹⁹ *Neem* seed oil has shown toxicity, which, as suggested, may be due to contamination with seeds of Persian lilac or *Melia azedarach*,¹ or due to aflatoxins. However, purified *neem* oil obtained by debittering, deodorizing, and

decolorizing is nontoxic,²⁰ suggesting the importance of developing chemical profiles of raw materials and isolated compounds, which could help in evaluating the possible toxic effect of a preparation by identifying its toxic compounds.

***Coccinia grandis* Linn. (Family: Cucurbitaceae)**

Latin: *Coccinia indica* Wight &
Arn, *Cephalandra indica*
(Naud)

Hindi: Kanduri, Kundru

Sanskrit: Bimbi, Bimba

English: Ivy Gourd

Tamil: Kovakai

Coccinia indica is a climbing or prostrate perennial herb found growing throughout India and the Indian subcontinent. All parts of the plant are used, including leaves, stem, fruits, and roots. The drug has traditionally been used for the treatment of skin problems, respiratory disorders, and for diabetes. *Coccinia indica* is well known in Bengal for the treatment of diabetes, where it is reputed to be an Indian substitute for insulin. It is considered to be very effective in reducing urine sugar levels.²¹ There are two varieties recorded—the wild variety with greenish bitter nonedible fruits and the cultivated edible variety *C. indica* var. *palmata* that is sold in the market as a vegetable. Fruits of *C. indica* var. *palmata* have been shown to have more potent hypoglycemic activity and are preferred over the wild variety for treatment of diabetes,²² although usually the wild bitter variety is preferred for use in medicine.²³

From the aerial parts of *C. indica* var. *palmata*, heptacosane, triacontane, cephalandrol, β -sitosterol, and the alkaloids—cephalandrines A and B—have been isolated. From the fruits, lupeol, β -amyrin, and its acetate—cucurbitacin B and pectin—have been isolated.²⁴ The fruit pectin has been shown to produce significant reduction in blood glucose levels.²⁵

The different parts of the plant have shown a varied response when tested for hypoglycemic activity. Root extracts, either aqueous or

alcoholic, have shown significant hypoglycemic effect in alloxan-diabetic rabbits^{26,27} and rats,²⁸ and in glucose loaded^{29,30} and fasted rats.³⁰

Alcoholic extract of the fruits inhibited in rats, though not significantly, the hyperglycemic effect caused by anterior pituitary extract³¹—corticotropin and somatropin.³² Decoction of fruits of *C. indica* W & A at 20 ml·kg⁻¹ showed significant hypoglycemic activity in glucose-fed fasted rabbits. The edible fruits of *C. indica* var. *palmata* was found to be more potent than that of *C. indica* W & A. Thus the fruit juice of the wild variety did not show any activity whereas the fruit juice of *C. indica* var. *palmata* at 20 ml·kg⁻¹ showed very significant activity ($p < 0.001$) at the end of the fifth hour.²² The pectin isolated from the fruits at 200 mg per 100 g body weight has been shown to reduce blood glucose levels in normal rats by enhanced glycolysis, glycogenesis, and decreased glycogenolysis.²⁵

Alcoholic extract of leaves of *bimbi* reduced blood sugar levels in guinea pigs³³ and streptozotocin-induced diabetic rats.^{34,35} Depressed synthesis of blood glucose was due to depression of the enzymes glucose-6-phosphatase,^{34,35} fructose-1,6-bisphosphatase, and enhanced glucose oxidation.³⁴

In a double-blind clinical trial, tablets made from freeze-dried leaves of *C. indica* were tried on 16 patients with uncontrolled maturity-onset diabetes in the treatment group, and 16 patients in the placebo group received placebo tablets made from chlorophyll. Patients received 3 tablets, weight of tablet not mentioned,³⁷ twice daily for 6 weeks. Ten patients on the drug showed significant improvement in glucose tolerance ($p < 0.001$), whereas none of the placebo group showed such marked improvement.^{36,37} Maximum effect was seen after 3 weeks, and no adverse effects were observed.

In an open trial, 41 patients with diabetes mellitus were treated with either *C. indica* powder or juice. Of these 24 were given 3 g of the powder twice daily with water before food for 5 weeks and 17 were given 30 ml drug juice, prepared from a fresh plant, twice daily before food. Response was seen within 7 days, evaluated based on reduction of blood sugar levels and relief of classical symptoms such as excessive urine, thirst, hunger, fatigue, numbness, and blurred vision. Excellent response was seen in 80 percent of the patients on powder and 47 percent on juice. No side effects were seen.³⁸

Along with the normal diet 50-100 g of *C. indica* powder per day was given to 100 hyperglycemic patients, in the age group of 25-70 years, and 60 healthy volunteers. Significant results were seen from the first week. Lowering of blood cholesterol, low-density lipoproteins, and serum triglycerides were seen with an increase in high-density lipoproteins.³⁹

Coccinia indica showed glycemic control in noninsulin-dependent diabetic patients, who did not respond to diet therapy alone. The drug showed moderate blood sugar lowering property that increased with use in subsequent months.⁴⁰

Dried aqueous extract of fresh leaves of *C. indica* was made into 3 g pellets, which were again oven dried and 1 pellet was given twice a day before food to 25 NIDDM patients. Group 1 was a control group of 15 healthy controls, Group 2 consisted of 30 untreated patients, and Group 3 consisted of 25 patients treated with *C. indica* and 15 with the oral drug "Diabenese" (chlorpropamide) for comparison. Diet was restricted and follow-up was done at 6-week intervals for two consecutive periods. The herbal drug was found to be effective in controlling both hyperglycemia and hyperlipidemia at the end of 6 weeks. Reduction of blood sugar in the *C. indica* group was comparable to Diabetese.⁴¹

To study the influence of *C. indica* on certain enzyme levels, dried extract of 50 mg·kg⁻¹ body weight·day⁻¹ of *C. indica* was given twice a day before food to 30 diabetic patients both IDDM and NIDDM for 6 weeks. Treatment significantly restored the reduced activity of lipoprotein lipase (LPL), and lowered the levels of glucose-6-phosphatase and lactate dehydrogenase (LDH), which are raised in severe diabetics. The authors postulate that the ingredients of *C. indica* extract act like insulin to correct the elevated levels of glucose-6-phosphatase and LDH in the glycolytic pathway, and restore the LPL in the lipolytic pathway with the control of hyperglycemia in diabetes.⁴²

Considering the positive results obtained, further trials are needed with a larger number of patients. In addition, the composition should be standardized in order to obtain consistent results. *C. indica* belongs to the Cucurbitaceae family. The fruits of the cultivated variety of *C. indica* are commonly eaten as a vegetable and therefore considered safe to use. In the clinical trials no side effects and toxicity were observed.^{37,38}

***Gymnema sylvestre* R. Br. (Family: Asclepiaceae)**

Sanskrit: Meshashringi

Tamil: Sirukurinja

Hindi: Gurmar

English: Periploca of the woods

Gymnema sylvestre (see Plate 11 in color gallery) is a woody climber found growing extensively in the southern and central parts of India. The leaves of the plant when chewed have the peculiarity of numbing the tongue so that one is not able to recognize sweet or bitter tastes. Hence the Hindi name *gurmar* that means destroyer of sweet (*gur*: sweet; *mar*: destroyer). This has been shown in humans to be owing to the presence of triterpene acids known as gymnemic acids and in rats due to a 35-amino acid peptide called gurmarin.⁴³ The leaves have been used for the treatment of diabetes for a long time. The plant is considered a stomachic, a stimulant, a diuretic, and a laxative. It is said to be useful in cough, biliousness, and sore eyes.⁴⁴

From the leaves of *Gymnema* several oleanane and dammarane triterpene saponins have been isolated and characterized. The best known of the oleanane triterpenoid saponins are the gymnemic acids that have been isolated from the aqueous extracts. Fractions containing gymnemic acids have shown hypoglycemic activity. Gymnemic acid IV has been shown to increase the plasma insulin levels in streptozotocin-diabetic mice.⁴⁵ Apart from these compounds flavones, anthraquinones, hentriacontane, pentatriacontane, resins, inositol, d-quercitol, lupeol, β -amyrin, stigmasterol, and some acids, for example, tartaric acid, formic acid, and butyric acid have been isolated and their structure determined.⁴⁶

There are a number of animal studies regarding the beneficial effect of *Gymnema* on diabetes. Administration of *gurmar* leaf powder to alloxan-diabetic animals regulates blood sugar levels^{47,48} inducing protracted longevity.⁴⁸ In addition to blood glucose homeostasis, enzyme activity controlling glucose utilization by insulin-dependent pathways was also increased.⁴⁷

In glucose-fed streptozotocin-diabetic rats glucose homeostasis was observed⁴⁹⁻⁵¹ by feeding leaf extracts possibly because of increased serum insulin levels⁵⁰ caused by regeneration of the islets of

Langerhans⁵¹ and/or by increasing cell permeability.⁵² It has been suggested that extracts containing gymnemic acids suppress elevation of blood glucose levels by inhibiting glucose uptake in the intestine.^{49,53} Gymnemic acid IV, but not gymnemic acid I-III or gymnemasaponin V, at dose levels of 3.4-13.4 mg·kg⁻¹ reduced blood glucose levels by 13.5-60 percent 6 hours after administration in a manner similar to glibenclamide. Also at 13.4 mg·kg⁻¹, plasma insulin levels were increased in streptozotocin-diabetic rats suggesting that this may contribute to the antihyperglycemic activity of the leaves.⁴⁵

Lipid abnormalities found in alloxan-diabetic animals was restored to near normalcy by feeding with the hypoglycemic leaf extract of *Gymnema sylvestre*.⁵⁴ This activity of the leaf extract given at 100 mg·kg⁻¹ in hypolipidemic rats for 2 and 10 weeks^{55,56} was found to reduce triglyceride and total cholesterol levels^{55,56} similar to clofibrate.⁵⁵ Gymnemic acid fractions containing 363.3 mg·g⁻¹ of gymnemagenin⁵⁷ and leaf extract⁵⁸ have been shown to increase excretion of fecal cholesterol and cholic acid-derived bile acids. In addition, gymnemic acids potentially inhibit absorption of oleic acid in the intestine.⁵⁹ Increased glycoprotein levels, which are considered the major cause of nephropathy, neuropathy, and retinopathy and found elevated in streptozotocin-diabetic rats, were brought under control by administration of leaf extract GS₄.⁶⁰

Clinical studies have been conducted using the leaf powder and concentrates from the leaves containing gymnemic acids. In an early exploratory trial, ten healthy normal persons and six diabetics with mild-to-moderate hyperglycemia were given an aqueous decoction of powdered leaf of *gurmar* at a concentration of 10 g per 100 ml. The dose was 2 g thrice daily for 10 days. After 10 days, there was a definite fall in blood glucose levels after glucose tolerance test, which was significant only in diabetics. Fasting blood glucose levels had fallen significantly both in normal and diabetic patients.⁶¹

The two studies used the concentrate named GS₄, obtained by extraction of the leaves with 50 percent aqueous ethanol^{51,60} precipitation with hydrochloric acid followed by recrystallization of the crystals with aqueous ethanol. In 22 NIDDM patients on conventional therapy, oral hypoglycemic drugs were supplemented for 18-20 months with 400 mg·kg⁻¹ of GS₄. During supplementation with GS₄, patients

showed a significant reduction in blood glucose, glycosylated hemoglobin, and glycosylated plasma proteins because of which the dosage of conventional drugs glibenclamide or tolbutamide could be decreased or stopped. Thus 5 of the 22 patients could stop conventional therapy and manage with GS₄ alone. During supplementation most of the patients reported a sense of well-being, better alertness, and less exhaustion when doing work.⁶²

GS₄ was administered orally to 27 IDDM patients along with their daily insulin injection for varying periods ranging from 2 to 30 months. None of the patients had symptoms of renal damage, retinopathy, or cardiovascular damage. These patients were compared with a control group of 37 patients on insulin therapy alone. Patients on GS₄ were able to reduce their insulin dose with reduction of blood glucose levels, glycosylated hemoglobin, and glycosylated plasma protein levels. Plasma lipid levels came back to near normal levels. In addition, there was a sense of well-being, an improved ability to do work together, and increased mental alertness. In the control group on insulin therapy alone, there was no significant decrease in blood lipid levels, fasting blood glucose, glycosylated hemoglobin, and glycosylated plasma proteins or serum amylase levels. Therapy with the *Gymnema sylvestre* extract GS₄ appears to enhance endogenous insulin, according to the authors, by regeneration or revitalization of the residual beta cells.⁶³

In another open trial, the hypoglycemic activity of *Gymnema sylvestre* leaf powder, at a dose of 10 g per day when administered for 7 days to 16 normal persons and 43 mild diabetics, was studied. After 7 days, 36 diabetics received tolbutamide, whereas the remaining seven diabetics received *Gymnema sylvestre* powder alone for 2 more weeks. Fasting blood sugar levels of the seven diabetics on *gurmar* powder for 3 weeks showed improved glucose tolerance. Lipid levels in normal persons remained unchanged, whereas in diabetics there was a significant decrease in total cholesterol, serum triacylglycerol, and free fatty acids. *Gymnema sylvestre* also showed a definite hypoglycemic effect in both normal subjects and in diabetic patients, and the effect in diabetics was evaluated as comparable to that of tolbutamide.⁶⁴

The water-soluble portion GS of the alcoholic extract of *Gymnema sylvestre* leaves, containing gymnemic acids (A-D) along with potassium

and magnesium ions obtained by fractionation of the extract using bioassay, was given orally at dose levels of 120-360 mg daily to 61 diabetic patients in the age group of 23-60 years. In 70 percent of the cases glucose homeostatis could be achieved using GS with results being seen in 2-4 weeks. The authors concluded that GS is useful in NIDDM patients who are poorly controlled by standard therapy. There was no abnormality in the biochemical investigations, such as blood count, hemoglobin, liver function tests, and nonprotein nitrogen, when carried out after 1 year of therapy.⁶⁵

Gymnema sylvestre leaves and stem are extensively used in Gujarat, India, for the treatment of diabetes.⁶⁶ Preparations of the leaves and extracts are widely available in Japan as health foods in the form of tea bags, tablets, beverages, and confectionary.⁵⁷ The leaves and stems have been considered nontoxic to human beings.⁶⁶ In a trial with *Gymnema sylvestre* extract known as GS₄ there were no undesirable side effects, such as nausea, vomiting, lassitude, or other gastrointestinal disturbances. Patients reported an increased sense of well-being and a few female patients experienced relief of pain in the limbs.⁶³ In a 1-year clinical trial, consumption of GS fraction from *Gymnema sylvestre* by type II diabetic patients showed no abnormality in blood count, hemoglobin, liver function test, and nonprotein nitrogen.⁶⁵ Rats that were fed extract powder of *Gymnema sylvestre* for 1 year in graded amounts ranging from 0.01 to 1 percent of diet were examined weekly up to 12 weeks, then at 26, and finally at 52 weeks showed no toxic effects at 1-percent level in the diet as seen from hematological, biochemical, and histological examination. In addition, there was no change in food consumption and in body weight.⁶⁷

***Momordica charantia* Linn. (Family: Cucurbitaceae)**

Sanskrit: Karabella

Tamil: Pavakka

Hindi: Karela

English: Bitter Gourd, Bitter
Melon

Momordica charantia is a slender climber with yellow flowers found growing throughout India. It is also cultivated countrywide for

its fruits, as it is a commonly eaten vegetable despite its bitter taste. The plant bears gherkin-shaped fruits with protuberances that are sold in the market when green, and there are several types available in different sizes big and small and shades of green.⁶⁸ The green fruits are sliced and dried in the sun to preserve them, in order to be consumed during the off season. The fruits are also popularly used for the treatment of diabetes, for which the cultivated variety of big fruits is used; the small fruits variety is generally preferred in medicine.⁶⁹ However, a study with two varieties of *karela* showed that the bigger fruits were more effective than the small, oval, dark-green fruits in alloxan-diabetic rabbits with mild ketosis.⁷⁰ The fruits, leaves, and roots have been commonly used as a folk remedy for diabetes. The fruits are considered a cooling bitter tonic, useful as a stomachic and carminative. They are also used for the liver and spleen and for gout and rheumatism.⁶⁸

A large number of compounds have been isolated from the fruits of *Momordica charantia*.⁷¹ The saponins and proteins are found to be important for the hypoglycemic activity. Of these the polypeptide known as p-insulin,⁷² (which has 17-amino acids and 166 residues, and has the same amino acid composition except for an extra methionine residue when compared to bovine insulin) and charantin,⁷³ (which is a steroidal glycoside mixture of sitosterol and 5, 25- stigmastadien-3- β -ol glucosides), and the triterpene glycosides—oleanolic acid 3-O-glucuronide and momordicin Ic⁷⁴ are considered responsible for the hypoglycemic activity although p-insulin itself does not act orally. Also contributing to the hypoglycemic activity is the pyrimidine nucleoside vicine,⁷⁵ which is found in the seeds. Other steroidal glycosides found in the fruit are momordicines and the cucurbitin glycosides—momordicosides.⁷¹

The hypoglycemic activity of the fruit and seeds has been studied extensively in different animal models⁷⁶⁻⁸⁵ and the work was reviewed in 1996.⁷¹ Fruit juice causes glucose tolerance in alloxan-diabetic rabbits but not in normal animals. P-insulin has been shown to be a very effective hypoglycemic agent when administered subcutaneously to gerbils, langurs, and humans.⁷² Charantin was found to produce a lowering of blood glucose concentration when administered either orally or intravenously.^{73,86} Oleanolic acid 3-O-glucuronide and momordicin 1 c exhibit

hypoglycemic activity by suppressing the transfer of glucose from the stomach to the small intestine, and by inhibiting glucose transport.⁷⁴ Intraperitoneal administration of vicine caused a hypoglycemic response in fasting albino rats.⁷⁵

Fruit juice causes significant ($p < 0.004$) increase in the number of beta cells in streptozotocin-induced diabetic mice,⁸⁷ although an earlier study reported lack of any significant effect on the ability to tolerate external glucose load in diabetic mice by administration of 10 ml·kg⁻¹ fruit juice for 30 days, which was attributed to the lack of viable beta cells capable of secreting insulin upon stimulation in order to exert its oral hypoglycemic effect.⁸⁸

Fruit juice of *Momordica charantia* has also been shown to be a potent scavenger of superoxide and hydroxyl radicals.⁸⁹ Four different preparations of *karela*—fruits, juice, seed extract, freeze-dried juice, and commercially available capsules showed that in healthy rats the hypoglycemic activity of fruit juice, freeze-dried fruit juice, and seed extract were comparable and they showed significant improvement in the ability to tolerate an oral glucose load, whereas commercial capsules did not significantly improve glucose tolerance.⁹⁰

Studies of rats with diets supplemented with 0.5-3.5 percent of freeze-dried powder of fruit for 14 days both in the presence and absence of dietary cholesterol showed that there was a marked reduction of hepatic total cholesterol, triglyceride levels, and an increase in HDL-cholesterol.⁹¹ In streptozotocin-diabetic rats, long-term feeding for 10 weeks of fruit extract brought elevated lipid levels back to near-normal values.⁹²

Fruit extracts of *Momordica charantia* when fed at 4 g·kg·day⁻¹ per rat to murine alloxan-diabetic rats retarded the formation of cataract. The *karela*-treated diabetic mice developed cataract in 140-180 days, whereas controls receiving 0.9 percent sodium chloride solution developed cataract in 90-100 days.⁹³ *Karela* extracts (200 mg·kg⁻¹) fed daily prevented, to a significant extent ($p < 0.05$), renal hypertrophy in diabetic rats.⁹⁴ Aqueous extracts of *karela* at 400 mg·day⁻¹ prevented, substantially, hyperglycemia and hyperinsulinemia induced by a high fructose diet.⁹⁵

Experimental evidence obtained so far suggests that *karela* exhibits its hypoglycemic activity through inhibition of glucose absorption⁹⁶ and

also tends to be extrapancreatic, independent of glucose absorption in the intestine.⁸⁰ Thus also seen in the experimental studies are increased utilization of glucose by the liver,^{83,97} inhibition of glucose synthesis while increasing glucose oxidation,⁹⁸ and decreased insulin resistance by increasing the amounts⁸⁴ of the transporter protein GLUT.⁸⁴ The depressed carbohydrate enzyme levels in the liver of diabetic mice were partially restored to normal,⁹⁹ whereas oxidative stress was reduced by normalizing disturbed glutathione S-transferase distribution.¹⁰⁰ Momordicin Ic and oleonic acid-3-O-glucuronolide inhibit transfer of glucose from the stomach to the intestine, and inhibit glucose transport to the brush border of the small intestine.⁷⁴ In addition, *karela* is shown to cause regeneration of beta cells in streptozotocin-diabetic rats⁸⁶ and exhibit an insulinomimetic or insulinogogue effect.¹⁰¹⁻¹⁰³

An experimental study in different animal models, using different doses, was carried out to find out the scope of use of *karela* in diabetes of varying intensity. The study showed that *karela* is best used for controlling hyperglycemia in mild-to-moderate noninsulin-dependent diabetics only. The extracts had no adverse effect on various hematological parameters. *Karela* extracts were found to differ from insulin in four ways—oral administration; a delayed onset with a sustained duration of action; increase in the peripheral utilization of action even in tissues that are insulin dependent, for example decrease of glycogen even in the kidney; and a longer duration of action.⁹⁹

Momordica charantia has been studied in small groups of patients by Vaclad, who noticed that blood sugar was significantly lowered in patients administered fresh fruit juice or tablets prepared from fruit powder.¹⁰⁴⁻¹⁰⁶

Inspired by reports of use of *karela* in diabetes^{107,108} and of its possible effect on the other drugs being consumed by diabetics, a study was carried out on nine NIDDM patients of Asian origin. Coadministration of a water-soluble extract of the fruits during a 50 g glucose tolerance test significantly reduced blood glucose concentrations without any influence on the insulin levels. Since *karela* is often eaten in the form of curry as part of the diet, the addition of fried *karela* fruits to the daily diet for 8 to 11 weeks was also investigated. This produced a small but significant improvement in the glucose tolerance with no

increase in insulin levels. In addition, there was a significant reduction in glycosylated hemoglobin levels.¹⁰⁹

Similarly a beneficial effect was seen in eight NIDDM patients given daily powdered *karela* fruit for 7 weeks. Improvement in glucose tolerance and fasting blood glucose levels was observed.¹¹⁰ There was a significant glucose tolerance in 73 percent of maturity-onset diabetic patients, who were administered fruit juice of *karela*, whereas the remaining 27 percent failed to respond.¹¹¹

Aqueous extract of fruit given for 3-7 weeks resulted in a significant fall in postprandial blood sugar levels. There was a marked fall in both the blood sugar and the urine sugar levels; the hypoglycemic effect takes place in a cumulative and gradual manner unlike that when using insulin. The aqueous extract, with a fall in blood sugar of 54 percent, was found to be more effective than the dried-fruit powder, with a fall in blood sugar of 25 percent, after 3 weeks of therapy. There was also significant reduction of glysoylated hemoglobin at the end of the trial.¹¹²

The effect of aqueous homogenized suspension of the green fruit pulp of *M.charantia*, given to 100 moderate NIDDM patients 2 hours after the intake of 75 g of glucose, was studied. There was a significant reduction ($p < 0.001$) in postprandial serum glucose levels in 86 percent of the patients and fasting glucose levels in 5 percent of the cases.¹¹³

In an open study in Germany, 41 NIDDM patients took a 500 mg capsule of *Momordica charantia* extract, containing at least 10 percent charantin, twice a day prior to the two main meals, for 24 weeks. In the group of patients considered to have moderate diabetes, with fasting glucose ≤ 200 mg·dl⁻¹ and HbA_{1c} ≤ 8.0 percent, the blood glucose levels fell by 25 percent and the HbA_{1c} by 0.5 percent bringing them into the classification of patients with glucose intolerance, and therefore less prone to late complications of diabetes. No adverse effects were noted during the course of the trial.¹¹⁴

P-insulin administered subcutaneously led to a significant hypoglycemic fall in six IDDM, one NIDDM, and two asymptomatic diabetics.¹¹⁵ In another study, subcutaneous p-insulin led to a significant fall in blood glucose levels in 11 IDDM patients; however, no significant effect

was seen in eight NIDDM patients. A single IDDM patient could be maintained on p-insulin for 5 months.⁷²

Momordica charantia fruits are commonly eaten as a vegetable in India with no untoward effects. However, it can cause loose motions and stomachache¹¹⁴ when consumed in large quantities, probably because of its bitter taste and its known laxative and emetic action.¹¹⁶ In a clinical trial to evaluate the safety and efficacy of an extract of *Momordica charantia*, no adverse effects were observed, leading the authors to conclude that the extract at the dose employed was a safe nutraceutical without any toxic side effects.¹¹⁴ Some adverse effects in animals have been reported, for example, changes in testicular function in dogs¹¹⁴ and uterine hemorrhage in pregnant rats,¹¹⁷ emphasizing the need for caution in use in pregnancy and supervision by a physician when coadministered with other drugs for diabetes in the context of the known synergistic effect with other antidiabetic drugs.^{108,114,118}

***Pterocarpus marsupium* Roxb. (Family: Fabaceae)**

Sanskrit: Asana, Beejaka	Tamil: Vengai
Hindi: Vijayasar, Bijasal, Bija	English: Indian Malabar Kino

Pterocarpus marsupium is a moderate-to-large-sized deciduous tree found commonly in the hills in south and central India. The tree yields one of the most important timbers of India. *Pterocarpus marsupium* is well-known for its use in skin diseases and in diabetes. The sapwood is pale-yellowish white to white and the heartwood is golden-yellowish brown in color, which stains yellow when it is moist;¹¹⁹ the yellow color is probably indicative of the flavonoids present in the wood. The heartwood of *Pterocarpus marsupium* is considered to be useful for diabetes and has been the subject of a multicentric clinical study undertaken by the Indian Council of Medical Research (ICMR) to establish its efficacy. (See later in this chapter.) In many parts of India, tumblers made of the heartwood of *Pterocarpus marsupium* are sold in the market, and diabetics drink water stored overnight in these tumblers

to control blood sugar levels. This folkloric use has been corroborated by a small clinical trial.¹²⁰

The heartwood is a rich source of flavonoids and other phenolic compounds.¹²¹ From the alkali-soluble portion of the heartwood were isolated isoliquiritigenin, liquiritigenin, and pterostilbene, and from the sapwood, pterostilbene.¹²² Other compounds from the heartwood are marsupin, pterosupin,¹²¹ marsupol, carsupin, propterol, and propterol B.¹²² The bark contains epicatechin and pterostilbene.¹²² Among the compounds considered to have hypoglycemic activity are epicatechin, marsupin, and pterostilbene. Pterosupin and liquiritigenin have been shown to be effective in reducing total cholesterol and lipid, and lipoprotein levels.¹²¹

The oral hypoglycemic activity of *Pterocarpus marsupium* has been studied in a number of experimental models, using aqueous infusion of *vijaysar* in acute hyperglycemic response caused by anterior pituitary extract in glucose-fed albino rats,¹²³ in alloxan-induced diabetic rats,¹²⁴ in normal,¹²⁵⁻¹²⁷ and alloxan-diabetic rabbits.¹²⁵ The aqueous extract was found to be more active than the alcoholic extract, and also found to be active in both acute and chronic experiments in normal rabbits. In addition, the aqueous extract showed a more potent hypoglycemic effect than *Gymnema sylvestre* and *C. indica*.¹²⁵ Administration of aqueous extract of *vijaysar* for 15 days resulted in reduced glucose absorption from the gastrointestinal tract, which was attributed to the action of tannates.¹²⁸ Other workers also reported similar findings of blood sugar lowering.^{129,130}

Pterostilbene from *vijaysar*, when administered intravenously to dogs, led to a fall in blood sugar at 10 mg·kg⁻¹, whereas higher doses led to an initial hyperglycemia followed by hypoglycemia. It also caused a fall in the blood pressure of anesthetized dogs and was found to be toxic at 30 mg·kg⁻¹.¹³¹ The flavonoid fraction and the pure component (-)-epicatechin of *Pterocarpus marsupium* was shown to cause regeneration of the beta cells of the pancreas, which was considered to explain its hypoglycemic action.¹³²⁻¹³⁴ Some other authors were unable to repeat these studies¹³⁵⁻¹³⁸, however, later studies have shown that (-)-epicatechin has insulogenic as well as insulin-like properties.^{139,140} In addition, epicatechin has been shown in vitro to enhance insulin release by conversion of proinsulin to insulin, which

was more pronounced in immature rat islets.¹⁴¹ Marsupin and pterostilbene on i.p. administration to streptozotocin-hyperglycemic rats significantly lowered blood glucose levels, the effect being comparable to metformin (1,1-dimethylbiguanide).¹⁴²

In order to work out a dose-response relationship, aqueous extract of *vijaysar* bark was administered to normal rats, glucose-fed hyperglycemic rats, and alloxan-induced diabetic rats. At 1 g·kg⁻¹ given orally there was significant ($p > 0.001$) reduction in blood sugar 2 hours after the administration of aqueous extract. In alloxan-diabetic rats, the aqueous extract of *vijaysar* on daily administration for 3 weeks produced a significant ($p < 0.001$) lowering of blood glucose levels, which is slow in onset, starting from the first week and progressing till the third week.¹⁴³ In addition, the aqueous extract has also been shown to exert an anticataract effect in alloxan diabetic rats.¹⁴⁴

The decoction of *vijaysar* bark extract showed hypocholesterolemic effect in rabbits.¹⁴⁵ The ethyl acetate extract of *vijaysar* administered for 14 days to rats with hyperlipidemia produced a significant reduction of serum triglyceride, total cholesterol, and LDL- and VLDL-cholesterol levels. Among the active constituents of the *vijaysar* bark extract are liquiritigenin and pterosupin.¹²¹

There have been a number of exploratory studies with small groups of patients. Only one open, multicentric trial has been reported by the Indian Council for Medical Research (ICMR) in 1998, which concluded that *vijaysar* was useful in the treatment of newly diagnosed or mild, untreated NIDDM patients.

In a preliminary open clinical trial, 1 dram of heartwood extract of *vijaysar* was given thrice a day, after the main meals, to 14 diabetic patients on insulin. After a washout period of 5 days, only one patient showed significant hypoglycemic activity. No side effects were observed. However, as part of the same study, the activity of *vijaysar* was compared with that of powdered seeds of *Eugenia jambolana* and it was found that 42 percent of patients responded at a dose level of 1 dram three times a day of *Eugenia jambolana* as compared to 7 percent patients responding to *vijaysar*.¹⁴⁶ It appears that *vijaysar* is not useful in IDDM patients.

The decoction of the bark extract of *vijaysar* was administered to 22 diabetic patients at different dose levels. Glucose tolerance improved

in 12 patients after 7 days of treatment.¹⁴⁷ In another open study, 250 mg capsules of dried aqueous extract, prepared by decocting the heartwood, was given to 35 diabetic patients. A favorable response was found only with respect to urine sugar, with little effect on blood sugar levels.¹⁴⁸ In another trial, 20 NIDDM patients were divided into two groups of ten patients each. After a washout period of 10 days, ten patients who were earlier on standard drugs such as chlorpropamide, tolbutamide, or phenformin had the drugs withdrawn and the patients were given 5 g *vijaysar* granules made from dried aqueous extract of *vijaysar* heartwood powder thrice a day for 3 weeks, whereas the other group of ten patients, who were freshly diagnosed with diabetes, were started straightaway on *vijaysar*. Both groups showed significant lowering of blood sugar. No major side effects were observed but two patients taking *vijaysar* had loose motions and gastric upset, controlled by reduction in the dosage.¹⁴⁹

Water stored overnight in a tumbler made of *vijaysar* heartwood is commonly used as a remedy for diabetes, as mentioned earlier. A small clinical trial was carried out with ten patients, who were given 200 ml of the water, which was stored in the tumbler overnight, twice a day for 1 month, taken after lunch, whereas water stored for the whole day was drunk after dinner. There was encouraging reduction of blood sugar from the second week of treatment and this hypoglycemic activity continued as long as the heartwood water was given.¹²⁰

In an open trial with two groups, patients were administered either 500 mg of *Saussurea lappa* extract twice a day or 100 ml of *Pterocarpus marsupium* decoction twice a day after meals for 30 days. Both drugs were found effective in the management of diabetes and no side effects were observed. There was a decrease in the mean postprandial blood sugar from the initial 283 mg percent to 241 mg percent after the treatment period, in patients treated with *Pterocarpus marsupium*. There was only a slight decrease in cholesterol levels.¹⁵⁰

An open, multicentric trial involving four centers and three dosage levels was carried out for 12 weeks to evaluate the efficacy of *vijaysar* in 97 newly diagnosed or untreated NIDDM patients. The aqueous extract, prepared by decocting the bark extract and evaporating it to dryness, was administered to patients. Patients were assessed based on blood glucose and glycosylated hemoglobin levels. It was found

that by 12 weeks, control of both fasting and postprandial blood glucose levels was attained in 67 of 97 (69 percent) patients studied. Blood sugar was controlled with an extract dose of 2 g in about 73 percent of patients, with 3 g in 16 percent of patients, and with 4 g in 10 percent of the patients. Four of the patients had to be withdrawn from the trial owing to excessively high postprandial blood glucose levels. The fall in both fasting and postprandial levels by 32 and 45 mg·dl⁻¹, respectively, after 12 weeks of treatment was significant ($p < 0.001$) starting from initial values of 151 and 216 mg·dl⁻¹. There was also a significant decrease ($p < 0.001$) in the glycosylated hemoglobin levels from 9.8 to 9.4 percent. There was no significant change in mean lipid levels. No side effects were seen and all other laboratory parameters remained stable during the treatment period. As a result of the trial it was concluded that *vijaysar* is useful in newly diagnosed cases of diabetes mellitus.¹⁵¹

Thus the drug seems to be effective with an adequate dosage and careful selection of patients—either newly diagnosed or untreated NIDDM patients. The drug requires further investigation. In clinical trials with *Pterocarpus marsupium* no side effects have been noticed,¹⁴⁹⁻¹⁵¹ except for loose motions and gastric upset.¹⁴⁹ In small animals, extracts of *Pterocarpus marsupium* showed no untoward effect in doses used to elicit hypoglycemic effect.^{126,132}

Salacia spp. (Family: Celastraceae)

Latin: <i>Salacia reticulata</i> Wight	Malayalam: Ekanayakam, Ponkoranti, Koranti
Sanskrit: Vairi, Pitika	
Latin: <i>Salacia oblonga</i> Wall ex Wight & Arn	Malayalam: Ponkoranti
Latin: <i>Salacia prinoidea</i> DC, <i>S. chinensis</i> Linn., <i>S. latifolia</i> Wall. ex M. Laws.	Malayalam: Cherukuranti. Trade name: Saptrangi
Latin: <i>Salacia macrosperma</i> Wight.	Malayalam: Anakoranti
Latin: <i>Salacia fruticosa</i>	

The genus *Salacia* is a group of climbing or creeping shrubs or small trees of which 18 species are found in India.¹⁵² Over five species are used in Ayurveda and Siddha for the treatment of diabetes—*Salacia prinoidea*, *S. macrosperma*, *S. oblonga*, *S. fruticosa*, and *S. reticulata*, that have varied locational distribution.¹⁵²⁻¹⁵⁴ Of these, the three most commonly used are *S. prinoidea* (= *chinensis*; *latifolia*), *S. oblonga*, and *S. reticulata*. *S. reticulata* is also one of the most widely used plants for diabetes in Sri Lanka.¹⁵⁵ Preparations of *S. reticulata* are sold in Japan as a food supplement for obesity and diabetes.¹⁵⁶ It is not certain from a study of literature whether carefully identified species have been used and, therefore, whether there are problems in the interpretation of results. Roots and root bark of *Salacia* species have been used in Ayurvedic medicine for the treatment of diabetes. Apart from this, the root has been used for treating itch, rheumatism, and venereal diseases, such as gonorrhea.¹⁵²

The xanthone mangiferin has been isolated from the roots of several *Salacia* species—*S. reticulata*,^{157,158} *S. oblonga*, *S. chinensis*, and *S. prinoidea*.¹⁵⁸ However, *S. chinensis* is considered a synonym for *S. prinoidea*.¹⁵² Also isolated from *S. reticulata* are catechin and catechin dimers. Potent alpha-glucosidase inhibitors, salacinol and kotalanol, have been isolated from both *S. reticulata*^{159,160} and *S. oblonga*.¹⁶¹ Several compounds—xanthone,¹⁵⁸ triterpenoids,¹⁶¹ diterpenoids,¹⁶¹ and flavonoids—with inhibitory effect on rat lens aldose reductase have been isolated from stems of *S. reticulata*, *S. oblonga*, and *S. chinensis*.^{158,161,162}

S. prinoidea

The hypoglycemic activity of infusion and decoction of root bark of *S. prinoidea* was studied in detail at different dose levels: 1g·kg⁻¹ bodyweight of infusion showed hypoglycemic activity comparable to tolbutamide.¹⁶³ Of the three *Salacia* species—*S. prinoidea*, *S. macrosperma*, and *S. fruticosa*, the infusion of *S. prinoidea* was found to exhibit maximum hypoglycemic activity at a dose of 1g·kg⁻¹ bodyweight. *S. fruticosa* did not have potent hypoglycemic activity, although *S. macrosperma* exhibited some degree of hypoglycemic activity.¹⁶⁴

S. oblonga

Two fractions derived from the petroleum ether extract of the root bark of *S. oblonga* showed 60 and 76 percent hypoglycemic activity of an equal dose of tolbutamide ($250 \text{ mg}\cdot\text{kg}^{-1}$) in albino rats.¹⁶⁵ *S. oblonga* root bark has significant blood sugar lowering activity and antioxidant property. Petroleum ether extract of root bark has also been shown to prevent streptozotocin-induced hyperglycemia and hyperinsulinemia, and produce a significant decrease in peroxidation products in streptozotocin-diabetic rats.¹⁶⁶ Aqueous methanolic extracts of *S. oblonga* inhibited the increase of serum glucose level in sucrose- and maltose-loaded rats. The aqueous portion of this extract containing potent alpha-glucosidase inhibitors salacinol and kotalanol, along with nine other sugars, inhibited alpha-glucosidase, whereas the ethyl acetate extract containing known di- and triterpenes and a new triterpene kotalagenin-16-acetate exhibited potent aldose reductase activity.¹⁶¹

S. reticulata

Salacia reticulata aqueous extract decoction of root bark fed at 1 ml per rat per day to fasting rats caused a 30-percent reduction of blood glucose levels, 3 hours after administration of the extract.¹⁵⁵ Aqueous extract of *S. reticulata* ($0.5\text{--}5 \text{ g}\cdot\text{kg}^{-1}$) reduced plasma glucose concentration in streptozotocin-induced diabetic rats; the effect being maximum at 1-5 hours after administration of extract.¹⁶⁷

Among the active constituents isolated is the xanthone mangiferin that has been shown to lower blood glucose levels in KK-Ay mice, an animal model for type 2 diabetes. Mangiferin has also been shown to improve hyperinsulinemia, possibly by decreasing insulin resistance,¹⁶⁸ and to exhibit alpha-glucosidase and aldose reductase-inhibitory activities.¹⁵⁸ Other active ingredients include salacinol and kotalanol, which are potent alpha-glucosidase inhibitors.¹⁵⁹⁻¹⁶¹

In India, *Salacia reticulata* is usually one ingredient of multiplant preparations in most products. Preparations of *S. reticulata* are available as herbal supplements for the treatment of obesity and diabetes in Japan. The extract, obtained by extraction of the roots with hot water have been shown to prevent postprandial increase in blood sugar in humans.¹⁶⁹ In

addition, it decreased fasting blood sugar, glycosylated hemoglobin, and body mass index in mild NIDDM patients.¹⁷⁰

As a single ingredient *Salacia prinooides* has undergone preliminary exploratory clinical evaluation and has been found to possess both hypolipidemic and hypoglycemic activity. Tablets of root bark of *S. prinooides* (*Ekanayakam*) 500 mg were given to 18 NIDDM patients (fasting serum glucose levels of 120-160 mg·dl⁻¹) at a dose level of 2.5, 3.5, and 5 g per day (six patients at each dose level), while six patients were kept as control with restricted diet just as the drug group. There was efficient lowering of blood glucose, mean serum cholesterol, and triglyceride levels, and increase in HDL-cholesterol levels without any side effects with *Salacia* treatment.¹⁷¹

In another open trial, 42 NIDDM patients were given either 500 mg tablets of *Salacia prinooides* alone or a 500 mg tablet of 1:1 mixture of *Salacia prinooides* and *Strychnos potatorum* for 2 months. A control group was managed with diet restrictions. Hypoglycemic and hypocholesterolemic activities were observed. There was a significant reduction in blood glucose levels; however, reduction in blood glucose levels was greater in patients who were on *Salacia prinooides* alone.¹⁷²

In another study, 25 patients were treated with 500 mg of *S. prinooides* (= *chinensis*) powder along with *triphala* tablets 2.5 g thrice a day for 6 months, which brought down blood sugar and urine sugar levels.¹⁷³ *Triphala* is a well-known Ayurvedic preparation containing, in equal proportions, dried fruits of *Terminalia chebula*, *T. belerica*, and *Phyllanthus emblica* and used as a bowel tonic.

There is an urgent need to conduct well-planned clinical trials to evaluate these potentially promising Ayurvedic drugs, and also to evaluate the relative efficacy of the different species.

Preparations with *Salacia reticulata* are available in the Japanese market, and as a combination drug with other plants in India. The safety profile of the hot-water extract of *Salacia reticulata* in terms of acute and subacute toxicity, mutagenicity, antigenicity, and phototoxicity have been carried out.¹⁷⁴⁻¹⁷⁶ In pregnant rats root extract of *S. reticulata* at a dose level of 10 g·kg⁻¹ significantly increased postimplantation losses, leading the authors to recommend that it should not be used in pregnancy.¹⁷⁷ However, the dose levels used seem to be high. The safety evaluation of hot-water extract of *Salacia oblonga* at ten times the normal in-

take for 2 weeks did not change the clinical chemistry or produce histological changes in rats.¹⁷⁸

***Syzygium cuminii* (L.) Skeels. (Family: Myrtaceae)**

Latin: *Eugenia jambolana* Lam.
E. cuminii Druce

Hindi: Jaman, Jam, Jamun

Sanskrit: Jambu

Tamil: Naval

English: Black Plum, Black Berry

Syzygium cuminii is a large evergreen tree found throughout India in the plains up to an elevation of 1,800 m,¹⁷⁹ that bears a large crop of subacidic, astringent fruits, which consist of an inner seed covered by a pink-to-purple pulp that can be eaten, that are sold in the market. Seeds of *jambu* have been used in India for a very long time for the treatment of diabetes although the fruit pulp and leaves are also used in other parts of the world. It is also a very common household remedy for diabetes, especially in the villages in South India either by itself or in combination with *Gymnema sylvestre*.

The bark extract decoction is used in gargling for sore throat, spongy gums and stomatitis, and for dysentery and diarrhea. Leaves are used for diarrhea, especially in children. The vinegar made from the fruits is used as a stomachic, a carminative, and a diuretic drug. The seeds of the fruit are used in diabetes, where it is considered to reduce the quantity of sugar in the urine and to allay thirst.¹⁷⁹⁻¹⁸¹

The seeds contain several phenolic compounds including gallic acid, ellagic acid, corilagin, substituted galloyl glucoses, caffeic acid, ferulic acid, quercetin, and the glycoside jamboline.¹⁸²⁻¹⁸⁴

There have been a number of studies on the hypoglycemic effect caused by seeds and seed extracts of *jambu*. Oral administration of seeds of *jambu* reduced blood sugar levels in different animal models^{185,186} comparable to chlorpropamide at doses ranging from 170 to 510 mg per rat,¹⁸⁵ and comparable to phenformin at a dose of 1 g·kg⁻¹ in casein diet in streptozotocin-induced diabetes in rabbits.¹⁸⁶ In addition, there was significant decrease in postmeal values of cholesterol, free fatty acids, and triglycerides comparable to phenformin.¹⁸⁶ Also observed was an in-

crease of cathepsin B activity both by plant extract and chlorpropamide reflecting possible proteolytic conversion of proinsulin to insulin.¹⁸⁵ An aqueous suspension of seeds of *jambu* was tested for hypoglycemic activity at different dose levels ranging from 1 g to 6 g·kg⁻¹ body weight in rabbits. The maximum hypoglycemic effect of 42.64 percent, which was shown at 4 g·kg⁻¹ dose level 3 hours after intake.¹⁸⁷ Aqueous, alcoholic, and acetone extracts of *jambu* seeds fed to albino rats at different doses for periods from 15 to 45 days produced significant hypoglycemic effect. The acetone extracts also reduced cholesterol and serum urea levels. In addition, blood sugar levels once lowered continued to be stable even for a fortnight after the treatment was stopped.¹⁸⁸ Oral administration of aqueous extracts of seeds of *jamun* (*jambu*) to alloxan-diabetic rats at a dose of 2.5 g and 5 g·kg⁻¹ body weight but not at the 7.5 g level for 6 weeks resulted in significant reduction of blood glucose levels, which was greater than glibenclamide. The extract also showed antioxidant activity but not at the 7.5 g level.¹⁸⁹ At 2.5 g·kg⁻¹ there was an increase in hepatic hexokinase activity and a decrease of glucose-6-phosphatase in alloxan-diabetic animals.¹⁹⁰

Free radical scavenging activity of the methanolic extract of *jambu* seeds and of the major constituent of the extract, gallic acid, showed free radical scavenging activity greater than ascorbic acid while that of the methanolic extract was comparable to ascorbic acid. The authors suggest that this free radical scavenging activity could be useful in prevention of cataract.¹⁹¹ This has been confirmed by another study that feeding lyophilized aqueous extract of the seeds at 200 mg·kg·day⁻¹ for 4 months prevented murine alloxan-diabetic cataract in rats.¹⁹²

Daily administration for 21 to 120 days of lyophilized aqueous extract of *jambu* seeds at 200 mg·day⁻¹ showed significant antihyperglycemic activity in mild-to-moderate degree of hyperglycemia, partially restoring altered skeletal and hepatic glycogen content and enzyme levels. Some degree of activity was also exhibited in severely diabetic mice (>400 mg·dl⁻¹).¹⁹³ At 400 mg·day⁻¹ for 15 days *jambu* extract prevented hyperglycemia and hyperinsulinemia induced by a diet high in fructose.¹⁹⁴ Renal hypertrophy was also prevented when fed at 200 mg·kg⁻¹ for 40 days when compared to diabetic controls.¹⁹⁵

Despite the popular usage of *jambu* seeds there are only a few open clinical trials. In an early trial on 28 patients 4-24 g of *jambu* seed

powder was given thrice a day. Twenty patients showed significant fall in fasting and postprandial blood sugar, seven showed decreases in postprandial blood sugar and an increase in fasting blood sugar, whereas one patient showed increases in both parameters. In addition, patients showed improvement in signs and symptoms of the disease. While there was no observable toxicity in the liver, kidney, and blood, side effects seen were nausea, diarrhea, and epigastric pain.¹⁹⁶

In an open clinical trial, 30 NIDDM patients were treated with 12 g of *jambu* powder given in three divided daily doses for 3 months. There was good control of blood sugar along with relief in symptoms that increased with duration of treatment. A control group of six patients were kept on chlorpropamide. Results with *Eugenia jambolana* were assessed as comparable to chlorpropamide. No side effects were observed.¹⁹⁷

A compound herbal preparation, consisting of 2 g each of powdered *Gymnema sylvestre* leaves and *Syzygium cuminii* seeds, was taken by 20 patients thrice daily for 6 weeks. Ten patients on restricted diets served as control. Seventy percent of the patients were found to have responded well, based on biochemical parameters and relief of symptoms such as frequency and quantity of urine, feeling of well-being, numbness and tingling of hand and feet, and itching. In addition, the response was considered good in 13.33 percent of patients, whereas the response was considered poor in 16.67 percent of patients. No side effects or toxicity was observed in rats.¹⁹⁸

The fruits of *Syzygium cuminii* are commonly and widely consumed in India; however, large quantities are not consumed because of the astringent nature of the fruits. In one clinical trial with *Syzygium cuminii* seeds, there were two cases of nausea, two of diarrhea, and one of epigastric pain.¹⁹⁶ Another trial, however, did not show any side effects and the drug was well tolerated.¹⁹⁷ Thus, clinical trials with standardized material and larger patient numbers are needed to obtain a clear picture of the safety and efficacy of the herb.

Trigonella foenum-graecum Linn. (Family: Fabaceae)

Sanskrit: Methika

Tamil: Vendium

Hindi: Methi

English: Fenugreek

Trigonella foenum-graecum is an annual herb found growing wild in Punjab, Kashmir, and the upper Gangetic plains. It is also cultivated extensively throughout India. Two types are known—a dwarf type used for culinary purposes and a tall type used for fodder. The seeds are common ingredients of curry, and the leaves are cooked and eaten as a vegetable. Dried leaves are sold in the market to add flavor and nutrition to food. The seeds are a common spice and also used medicinally. The seeds are aromatic, bitter, carminative, tonic, and a galactagogue. Internally it is used for inflammation of the gastrointestinal tract, for diarrhea, and dysentery probably because of the mucilage present in the seeds.¹⁹⁹

The seeds are a rich source of dietary fiber with 45-60 percent total carbohydrates, mostly as soluble fiber present as mucilage, 20-30 percent protein, and 10 percent of fixed oil. There are also several steroidal saponins in the seeds. The bitter taste of the seeds is because of the presence of furostanol saponins. Also present are sterols, flavonoids, alkaloids such as trigonelline, 0.015 percent of an essential oil,²⁰⁰ and amino acids including the novel insulin secreting amino acid 4-hydroxyisoleucine.²⁰¹

A number of studies have been carried out in small animals to find out the scope of hypoglycemic activity. An antidiabetic effect has been shown in rats, dogs, and mice.²⁰²⁻²⁰⁴ In alloxan-diabetic rats fenugreek extract^{205,206} and its major alkaloid trigonelline²⁰⁶ produced a significant hypoglycemic effect. Pretreatment with fenugreek prior to production of diabetes by streptozotocin improved both blood glucose and lipid levels.²⁰⁷ The antidiabetic and hypocholesterolemic activity of fenugreek has been reviewed in 1998.²⁰⁸

Fenugreek seeds brought back altered creatinine kinase activity in the heart, skeletal muscle, and liver of diabetic rats back to normal values.²⁰⁹ Changes in hepatic and renal glucose^{210,211} and lipid metabolizing enzymes²¹¹ were also normalized. Fenugreek seeds have been shown to have an antioxidant effect.²¹² The hypocholesterolemic activity has been reported by several authors.²¹³⁻²¹⁷ Fenugreek is considered to exert its antidiabetic effect in different ways—through its fiber content in a manner similar to guar gum both being rich in galactomannans,^{208,220} through inhibition of intestinal glucosidase²¹⁸ and through insulin release by 4-hydroxyisoleucine.²⁰¹ Trigonelline

was subsequently shown not to be active by administration in amounts present in fenugreek.²¹⁹

A number of small clinical trials have been conducted to evaluate the hypoglycemic activity of fenugreek. The hypoglycemic activity of fenugreek seeds and leaves was tested in normal subjects and diabetic patients. In an acute study on healthy volunteers, a single dose of various forms of fenugreek were tried out—25 g seeds, 5 g gum isolate, or 150 g leaves being given, the seeds being administered in four different forms—as whole seeds, defatted seeds, degummed seeds, and cooked seeds. Although the gum isolate and leaves showed no hypoglycemic effect, maximal reduction of blood glucose was shown by whole seeds. Therefore, in NIDDM patients 25 g of fenugreek seed powder in two divided doses was mixed with their usual diet for 21 days. There was significant reduction in blood glucose levels and insulin response. In addition, there was significant reduction ($p < 0.05$) in 24-hour urinary glucose output and in cholesterol levels.²²⁰

In type I diabetics, 100 g of defatted fenugreek, given in divided doses at lunch and dinner for 10 days, significantly reduced fasting blood sugar, improved glucose tolerance, reduced 24-hour urinary glucose excretion by 54 percent, and also showed a significant hypolipidemic effect.²²¹ A similar study in 15 NIDDM patients, who were fed randomly meals in cross-over design and incorporated with or without 100 g of defatted fenugreek seed powder, produced similar results.²²² Also in type II diabetics, fed with 15 g of fenugreek seed powder soaked in water per day, there was postprandial lowering of blood sugar level.²²³

In a cross-over study to determine whether the improved glucose tolerance was owing to the effect of fenugreek on the absorption or metabolism of glucose, the diet was either randomly incorporated with 25 g of fenugreek seed or left out in ten NIDDM patients as pretreatment for 15 days prior to intravenous glucose load. Results showed that the addition of fenugreek to the diet significantly reduced the area under the plasma glucose curve and increased glucose clearance, suggesting that improved peripheral glucose utilization contributes to improved glucose tolerance. Fenugreek also significantly increased molar insulin binding sites of erythrocytes.²²⁴

Studies have also been conducted to observe the hypolipidemic effect of fenugreek seeds in diabetic patients, who are known to be at risk of developing cardiovascular disease. An open long-term study was carried on 60 NIDDM patients to study the effect of fenugreek on lipid levels. There was an initial control period of 7 days followed by an experimental period of 24 weeks when patients consumed 25 g of fenugreek seed powder in two divided doses as soup in water before lunch and dinner. There was a significant fall in total cholesterol, LDL, and VLDL cholesterol, and also in triglyceride levels.²²⁵

A double-blind placebo-controlled study was conducted in order to evaluate the effects of fenugreek on glycemic control and insulin resistance in newly diagnosed mild-to-moderate NIDDM patients. In the treatment group, 12 patients received 1 g·day⁻¹ of aqueous alcoholic extract of fenugreek seeds, whereas the control group of 13 patients received placebo capsules for 2 months along with diet and exercise. Patients were randomly assigned either to treatment group or to placebo group. Both groups were checked to make sure they had similar baseline values. At the end of 2 months both the fasting and after meal blood sugar levels were comparable in the two groups. However, area under curve of blood glucose and insulin was significantly ($p < 0.001$) lower in the treatment group. There was also a decrease in insulin resistance and a significant decrease in triglyceride and increase in HDL cholesterol.²²⁶

Fenugreek seeds are a commonly used spice in Indian cooking and the leaves are used as a vegetable. In clinical trials, generally, no side effects have been reported at lower dosage levels of 15-25 g seed;^{223,224} however, with 100 g of fenugreek four patients complained of diarrhea and flatulence.²²¹ In subsequent trials, a few patients had GI disturbances even at 25 g.^{225,226} In a long-term study lasting 24 weeks, on diabetic patients who were administered 25 g of fenugreek seeds per day, there was no toxicity in the liver and kidney and no abnormality in blood parameters.²²⁷

No toxicity was observed in a short-term study of 90 days when rats were fed with equivalent of two and four times the human dosage of 25 g of fenugreek seeds, which is generally used in NIDDM patients to improve glucose tolerance and lipid levels. Liver function tests were normal as were liver histology and blood picture.²²⁸

NOTES

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OTHER PLANTS

Cinnamomum tamala Nees & Eberm. (Family: Lauraceae)

Sanskrit: Tamalapatra, Tejpatra	Tamil: Talishapattiri
Hindi: Tejpat	English: Indian Cassia Lignea

Cinnamomum tamala leaves known as *tejpatra* are used in Indian kitchens to add flavor to rice dishes, such as pulav. In a study on 32 NIDDM patients with mild to moderate diabetes, two heaped teaspoons of *C. tamala* leaf powder was given orally four times a day 0.5 hour before breakfast, lunch, tea, and dinner to find the effect on fasting blood sugar, glucose tolerance, and immediate response to intake of the drug. Eight patients were kept as control with no treatment except for a restricted diet of 1,800 calories. After 1 month, the control group showed a minor significant rise ($p < 0.01$) in blood sugar levels, whereas there was a significant fall in fasting blood sugar ($p < 0.001$), in the treated group. It was also possible to show that the drug lowers blood sugar level after glucose load.

In a third experiment on seven patients to see the immediate effect of 20 g of *C. tamala* on fasting blood sugar, the drug was given after collection of fasting blood samples. It was seen that the fall in blood sugar started half an hour after the intake of *Cinnamomum tamala*, and the decrease continued upto 2 hours. The fall was significant at all points ($p < 0.01$).¹ A radioimmunoassay study on five patients, to determine insulin levels in addition to fasting blood sugar levels, showed that fasting blood sugar dropped from 186 ± 42.34 mg percent before intake to 129.9 ± 25.39 mg percent at the end of 2 hours, whereas insulin levels changed from 16.83 before intake to $31 \mu\text{u}\cdot\text{g}^{-1}$ at the end of 2 hours. When two heaped teaspoons of the drug were taken for 15 days there was a significant fall in blood sugar levels (168.4 ± 25.25 to 111.8 ± 17.6 mg percent) after treatment. There was also a rise in insulin levels, which was not significant.²

Experimentally a 50-percent ethanolic extract of the leaves of *C. tamala* significantly reduced the plasma glucose levels both in normal and streptozotocin-diabetic rats. In addition, the extract was able to prevent rise in cholesterol and triglycerides in diabetic rats.³

Clerodendron phlomidis Linn. (Family: Verbenaceae)

Latin: *Clerodendrum multiflorum*
(Burm. f) O. Kuntze
Clerodendrum phlomidis Linn. f

Tamil: Thaludalai, Takkari

Sanskrit: Tarkaari, Vaijayanti

Hindi: Arni

In a study, 23 patients were divided into four groups. In the first group a 1:4 decoction prepared from 15-30 g of *Clerodendron phlomidis* was administered to 13 diabetic patients in daily divided doses for 5 weeks. In the second group of three patients, 500 mg of tolbutamide was given every day. The third group was given 30 units of insulin daily, whereas the fourth group was kept as control with no medication and controlled diet. *C.phlomidis* treatment led to a response in 46 percent of the patients. There was a reduction of blood sugar, urine sugar, and improvement in symptoms and in glucose tolerance. The mean percentage fall of blood sugar with *C.phlomidis* as compared to tolbutamide was 7.1 versus 11 percent, whereas the fall in urine sugar was 18.2 versus 22.2 percent. No side effects were observed.⁴

Phyllanthus amarus Schum & Thonn.
(Family: Euphorbiaceae)

Sanskrit: Bhumiyamalaki,
 tamalaki

Tamil: Keelanelli

Hindi: Bhuiavala

In a clinical study on 25 patients with moderate to severe diabetes (250-400 mg per 100 ml) 1 g of *Phyllanthus amarus* led to statistically significant lowering of blood sugar levels when given thrice a day for 3 months.⁵ In another study, a preparation of whole plant of *Phyllanthus amarus* was given for 10 days to nine mild hypertensives, four of whom were diabetic. There was a significant reduction in systolic blood pressure in nondiabetic hypertensives and in women. Also blood glucose levels was significantly reduced in the treated group.⁶

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DIABETIC COMPLICATIONS

Diabetic foot

One of the late complications of diabetes is the “diabetes foot,” which arises due to diabetic neuropathy, and not as thought earlier due to arterial complications, and results in a nonhealing, painless foot ulcer, which wrongly treated can lead to amputation.

***Rubia cordifolia* Linn. sensu Hook. f (Family: Rubiaceae)**

Sanskrit: Manjistha	Tamil: Manjitti
Hindi: Manji, Majit	English: The Indian Madder

Rubia cordifolia or *manjistha* has traditionally been used both internally and externally for the treatment of burns, wounds, fractures, bruises, insect bites, etc. *Rubia cordifolia* has potent antioxidant and anti-inflammatory activity. This has been made use of in the treatment of nonhealing diabetic foot ulcers (DFU).

In an open comparative clinical study, 100 patients, with nonhealing DFU of 20-30 months duration, were divided into two groups of 50 each. Group I was given oral antibiotics for systemic use along with antiseptics for topical use together with pentoxifylline 400 mg thrice a day. Group II was treated by dipping the ulcer in *Rubia cordifolia* extract and also by applying it topically as ointment. In addition, 500 mg of *Rubia cordifolia* and *Bauhinia variegate* (*kanchanara*) was given orally thrice a day for 3-4 months. General health, arterial circulation, ulcer margin measurements, radiological, biochemical, and microbiological assessments were done every month.

Recovery in group I on antibiotics was moderate and 60 percent underwent amputation, whereas group II showed very good recovery with only 10 percent partial amputation.¹

Diabetic neuropathy

In patients of confirmed diabetic neuropathy, *Sida cordifolia* was given and found to help in the management of diabetic nerve problems. Further details are not available.²

Diabetic retinopathy

Asparagus racemosus Willd. (Family: Liliaceae)

Another complication of diabetes is the effect on the vision or diabetic retinopathy. *Asparagus racemosus* or *shatavari*, which was described earlier in Chapter 3 for use in peptic ulcer, is also considered in Ayurveda to improve the vision (*chakshushya*). In an exploratory open trial, 30 diabetic patients were daily given 3 g of *Asparagus racemosus* root powder with water for 3 months, in addition to the antidiabetic treatment they were taking. It was found that there was absorption of vitriol and retinal hemorrhages, as well as soft and hard exudates. There was also improvement in parameters, such as venous dilation, microaneurysm, and neovascularization. According to the authors the drug had helped reduce changes of diabetic retinopathy and also helped in preventing further development of lesions as a result of diabetic retinopathy.³

NOTES

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Chapter 12

Central Nervous System Agents

The importance of the psyche in the cause of disease and in the maintenance of health has been recognized in Ayurveda, and plants have often been used to treat the Central Nervous System (CNS) disorders and retain mental ability even at a ripe old age. There is a sophisticated system of classification in Ayurveda based on pharmacological properties, and there are several categories described, including some with no equivalents in modern pharmacology.¹ Among the several kinds of CNS drugs described in Ayurveda, the most important and closely related to the Ayurvedic categories are—neuroleptics, hypnotics, analgesics, antipyretics, anxiolytics, memory enhancers, etc.² About 85 drugs have been listed under different groups and some in more than one.³

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MEMORY AND LEARNING ENHANCERS

Unique to Ayurveda are the so-called *medhya rasayana*, which were used to enhance memory and intellect, and to reduce anxiety due to stress. The Sanskrit *medhya* is derived from *medha* meaning intellect and therefore promoting mental function. *Rasayanas* are considered to be rejuvenators used to maintain health and modify the ill effects of aging. Several such plants that promote memory and learning have been described in Ayurveda. A few of them have been investigated to some extent and are described in the following section.

***Bacopa monnieri* (Linn.) Pendell (Family: Scophulariaceae)**

Latin: <i>Bacopa monniera</i> (Linn.) Wettst, <i>Herpestis monniera</i> (Linn.) HBK	Hindi: Brahmi
Sanskrit: Brahmi	English: Thyme-Leaved
Tamil: Nirparami	Gratiola, Water Hyssop

Bacopa monnieri is a small herb with pale lilac flowers found growing throughout India in moist areas. The name *brahmi* probably refers to Brahma's wife Brahmi—the Goddess of Learning—Saraswati—and therefore to its traditional use in improving retention and enhancing memory, and thereby intellect. Two plants often go under the name *brahmi*—*Bacopa monnieri* and *Centella asiatica*, and the two plants are the most commonly used *medhya rasayana* or mental rejuvenators; however, *Bacopa monnieri* is considered more powerful since it is used in the treatment of epilepsy and insanity, whereas *Centella asiatica*, known as *mandukaparni* in Sanskrit, is considered a general mental tonic because it is also used in small amounts as a vegetable^{1,2} in food items such as salads, chutneys, and tea. *Bacopa monnieri* whole plant has the official status in the *Indian Herbal Pharmacopoeia*, 2002, as a brain tonic.³

Chemical investigation of *Bacopa monnieri* has led to the isolation of several triterpenoid saponins of which Bacoside A, which is a mixture of

several saponins and Bacoside B, are considered to be the active constituents responsible for the memory-enhancing properties of the herb.^{3,4} Bacoside A is a mixture of Bacoside A₁—a minor component—Bacoside A₂, and Bacoside A₃—which has been shown to be a potent inhibitor of superoxide.^{5,6} Other components include hirsaponin, betulinic acid, alkaloids, flavonoids, and phytosterols³—a number of other constituents have been isolated from the plant as well.

Initial experimental studies focused on the antianxiety effects of the herb, which acting as tranquilizer led to improved mental functioning and better retention.^{7,8} Subsequent studies conducted with the alcoholic extract of the plant or with a standardized extract have demonstrated improved learning performance of rats in various stressful conditions.^{4,9} In addition, *Bacopa monnieri* mitigates the amnesic effect of stressors, for example scopolamine, stress, electroconvulsive shock,¹⁰ phenytoin,¹¹ and morphine.¹² In aged rats *Bacopa monnieri* slows down memory loss at 1 mg per 100 g body weight taken once a day,¹³ and in animal models of Alzheimer's disease, it has a memory-promoting effect.¹⁴ Several groups of authors and researchers have demonstrated the antioxidant properties of *Bacopa monnieri*.¹⁵⁻¹⁷ In addition, the free radical scavenging and protective effect of *Bacopa monnieri* is suggested to be mediated through the reduction of high concentrations of nitric oxide produced by astrocytes in Alzheimer's disease, ischemia, and epilepsy.¹⁸ Among the active constituents, Bacoside A₃ has been shown to be a potent inhibitor of superoxide with Bacopasaponin C showing less potent activity, whereas the two other remaining mixtures after isolation were not active.⁶ A standardized extract of *Bacopa monnieri* has been shown to exhibit antistress activity¹⁹ by modulation of expression of cells involved in the brain.²⁰ Also *Bacopa monnieri* extract exhibits an antidepressant effect in experimental models of depression in rats.²¹

It is only in recent years that the interest in *Bacopa monnieri* has increased with more information becoming available. Initial clinical trials were carried out in the 1980s on the antianxiety effect on patients with anxiety neurosis.

In an open trial, 35 patients with anxiety neurosis were daily given 30 ml of *Bacopa monnieri* made into syrup in two divided doses (equivalent to 12 g crude drug) for 1 month. Patients were assessed

weekly based on clinical relief, psychological, physiological, and biochemical changes. Treatment resulted in the reduction in anxiety levels apart from significant reduction in symptoms, resulting in improved mental function, assessed as mental fatigue and immediate memory span. There was also reduction in the levels of urinary vanillyl mandelic acid (VMA) and corticosteroids being excreted.²²

In another open trial, 36 subjects were divided into two groups: 18 normal subjects and 18 patients with anxiety neurosis. All subjects received one 500 mg capsule containing *Bacopa monnieri* extract equivalent to 2.5 g of dried drug thrice a day for 4 weeks. Treatment with the drug led to significant improvement in anxiety levels and depression, mental fatigue, and memory span, apart from effects on systolic blood pressure and rate of expiration. Patients also reported significant improvement in nervousness, palpitation, headache, and insomnia. Response to the drug was more pronounced in patients than in healthy volunteers.²³

In a safety and tolerability study conducted in a double-blind placebo-controlled noncross-over manner in 31 healthy human volunteers, single doses of 20-30 mg of Bacosides A and B, as well as multiple doses of 100-200 mg, were well tolerated. No untoward reactions or side effects were seen.²⁴

In another study carried out in double-blind placebo-controlled independent group design in order to examine the acute effects of *Bacopa monniera* extract on cognitive function in 38 healthy humans, the subjects were assigned to one of the two kinds of treatment: either 300 mg *Bacopa monniera* extract ($n = 18$) or placebo ($n = 20$). Testing, carried out before the intake of drug and 2 hours after, showed that there was no acute effect at the dose given.²⁵

In a similar double-blind placebo-controlled independent group design, the chronic effects of administration of 300 mg of *Bacopa monniera* extract or placebo for 5 weeks and 12 weeks was studied. Neuropsychological testing done at baseline, after 5 weeks and after 12 weeks showed significant improvement in the speed of visual information processing, enhanced learning rate, and memory consolidation, and improved anxiety state in the *Bacopa monniera* extract group as compared with the placebo group. Improvement was maxi-

mal at 12 weeks suggesting that *Bacopa monniera* exerts a favorable influence on learning and memory.²⁶

In a double-blind randomized placebo-controlled trial, the chronic effects of administration of *Bacopa monnieri* extract was studied in 76 adults enrolled in the trial. Testing of various memory functions and the level of anxiety was done at baseline, at the end of 3 months of the trial, and 6 weeks after the end of trial. The results showed that the rate of learning was unaffected, but there was a decrease in the rate of forgetting newly learned matter.²⁷

In a single-blind trial, 40 children aged between 6 and 8 years were divided into two groups. One group of 20 children were given 1.05 g *Bacopa monnieri* drug made into syrup (1 teaspoon containing equivalent of 350 mg *Bacopa monnieri*) thrice a day for 3 months, whereas the other group received placebo syrup. At the end of the treatment period, there was improvement in immediate memory and perception, and in the children's general performance.²⁸

In a study to test the safety and tolerability of Bacosides A and B, no side effects were seen, and the drug was well tolerated.²⁴ Further the effect of acute²⁵ and chronic²⁶ administration (12 weeks) of 300 mg of *Bacopa monnieri* extract on cognitive function in healthy volunteers was studied in a double-blind placebo-controlled manner. Adverse effects in the chronic study were not very different from placebo, only a greater percentage in the *Bacopa monniera* group reported dry mouth, nausea, and fatigue.²⁶

***Centella asiatica* Urban (Linn.) (Family: Apiaceae)**

The use of *Centella asiatica* (see Plate 8 in color gallery) in chronic venous insufficiency is covered in Chapter 6, "Cardiovascular drugs" and for wound healing in Chapter 9, "Dermatological agents." However, the herb is best known in India as a *medhya rasayana* or mental rejuvenator, which improves memory and retention. *Medhya rasayana* reduce the negative impact of stress by their mild tranquilizing action and by improving memory span and "intelligence."²⁹ The plant is also considered a rejuvenator or *rasayana* helping to maintain youthful vigor and vitality. It is used in the treatment of epilepsy, senility, and premature aging.³⁰ The leaves and the plant have been used for this purpose for a very long time, often taken in food in the form of spiced

paste of the leaves known as chutneys, in salads, or as tea to improve vigor, and as a brain tonic. Interestingly, it is given to children learning the *Vedas* in *Veda Patashalas*,³¹ or the traditional schools, where the *Vedas* are taught in the traditional manner of memorizing the vast number of *Vedic* verses solely by loud repetition and memorization. It is also a favorite, nowadays, with school children as examinations approach, to help in building memory and retaining the studied material. It is an official drug in the *Indian Herbal Pharmacopoeia*, 2002, as a brain tonic and sedative.³²

As with other *medhya* drugs, the first experimental studies investigated the sedative and antianxiety effects of the herb; since a calm mind helped in learning. Thus, the saponin fraction containing brahmoside and brahminoside was shown in rats to act as a mild tranquilizer.³³ Several extracts, including the alcoholic³⁴⁻³⁶ and aqueous extracts, showed potentiation of barbiturate or phenobarbitone hypnosis.³⁴ An experimental study in rats on the effect of 100 mg per 100 g body weight of an alcoholic extract of *Centella asiatica* on various neurotransmitters showed decreased levels of acetylcholine and increased levels of histamine and catecholamines, relative to a control group, suggesting that this may contribute to the antianxiety effect seen clinically.³⁶ In addition, the alcoholic extract showed a dose-dependent increase in gamma amino butyric acid (GABA) levels in rats that was blocked by the specific GABA_A blocker—bicuculline methiodide.³⁷ In vitro *Centella asiatica* has shown affinity for GABA_B receptor, which may contribute to memory enhancement.³⁸ The aqueous extract of *Centella asiatica* (25 mg·kg⁻¹ i.p.) showed, in small animals, an anti-anxiety effect comparable to diazepam³⁹ and the alcoholic extract injected intraperitoneally showed a mild sedative effect.⁴⁰

An experimental study on the effect of an aqueous extract of fresh *Centella asiatica* leaf was studied in small animals (albino rats) using a two-compartment passive avoidance task. In drug-treated animals, there was a significant improvement in 24-hour retention when compared to controls treated with saline. A study of the levels of central neurotransmitters norepinephrine, dopamine, and 5-hydroxytryptamine and their metabolites showed a significant decrease in the drug-treated group suggesting that these neurotransmitters help in the learning process mainly through inhibition. In addition, there is a decrease in the urinary

level of the metabolites homovanillic acid and 5-hydroxyl indole acetic acid.⁴¹ *Centella asiatica* aqueous extract has cognition-enhancing effect⁴² by virtue of its antioxidant activity.^{42,43} The aqueous extract has also been shown to reduce the amnesic effects of pentylenetetrazole.⁴⁴ In an animal model for Alzheimer's disease, the aqueous extract of *Centella asiatica* was able to prevent cognitive deficits and oxidative stress.⁴⁵

In a double-blind placebo-controlled study, 30 mentally retarded children were administered 0.5 g per day of the plant powder for 12 weeks. There was significant improvement in the general ability of the children and also in their behavioral pattern.⁴⁶ In a 6-month, double-blind trial in 30 mentally retarded children aged between 7 and 18 years given one 500 mg tablet of *Centella asiatica* (part not mentioned, probably whole plant powder as used by the same group in other trials) daily for 6 months, there was a significant increase in the general mental ability, overall adjustment, and mental concentration seen at the end of 6 months. This improvement in general behavior was maintained up to 1 year after withdrawal of the drug.⁴⁷ In a double-blind study, 57 normal children with an IQ between 90 and 110 were given 0.5 g of the plant powder for 1 year. There were 14 dropouts and data from 43 children was evaluated. It was found that there was no significant improvement in the intelligence quotient.⁴⁸

In another open trial with 12 educable, mentally retarded children, in the age group of 8-12 years, were given 100 mg·kg⁻¹ body weight of powder of *Centella asiatica* in two divided doses for 6 months and followed up for 1 year. Posttreatment values on Malin's Intelligence scale for Indian Children (MISIC), Bender's Gestalt Test, and Raven Matrices showed modifications at various mental levels. There was a very significant improvement in the academic performance of eight children.⁴⁹

In a double-blind placebo-controlled trial to test the anxiolytic activity, subjects were randomly assigned to receive either a single dose of 12 g of *Centella asiatica* ($n = 20$) or placebo ($n = 20$), and the acoustic startle response (ASR) was tested 30 and 60 minutes after the treatment when *Centella asiatica* was found to attenuate the ASR, suggesting that it has an anxiolytic effect.⁵⁰

Further clinical studies are needed to fully delineate the usefulness of this very promising plant and also to establish its effect on other

body systems and side-effect profile. The plant is generally considered safe and is commonly used in food. However, it is traditionally consumed only in moderate amounts; larger amounts are considered to cause headache and dizziness.⁵¹ There are also reports of photosensitivity when consumed. In animal experiments on mice no mortality was observed up to 5 g·kg⁻¹. The alcoholic extract was found nontoxic up to 350 mg·kg⁻¹ intraperitoneally.⁵²

***Celastrus paniculatus* Willd. (Family Celastraceae)**

Sanskrit: Jyotishmati	Tamil: Valuluvai
Hindi: Malkanguni	English: Black Oil Plant, Climbing Staff Tree, Intellect Tree

Celastrus paniculatus is a large, woody climber bearing yellow fruits found growing almost all over India up to 1,800 m. The fruits are capsules containing 3-6 seeds with an unpleasant odor and taste, enclosed in a red aril. The seed oil, known as *Celastrus* oil or *malkanguni* oil varies in color depending upon the method of processing: pale yellow—on cold expression, dark brown—when obtained by extraction with hexane, or black—if heat is used in the extraction process.^{53,54} In Ayurveda, the seeds and seed oil of *Celastrus paniculatus* are most commonly used in mental disorders and are considered to enhance memory and comprehension.⁵⁴ The fruits, including the seeds, have an official status in the *Indian Herbal Pharmacopoeia*, 2002, as a tranquilizer.⁵⁵

The seed contains 42-45 percent of fatty oil consisting of palmitic, oleic, linoleic, and linolenic acids and their glycerol esters. Also present in minor amounts are sesquiterpene polyesters—of which malkangunin is the major component—sesquiterpene alkaloids, and triterpenoids.⁵⁵ Experimental studies have shown sedative and tranquilizing action^{56,57} of the seed oil. The effects of the seed extract on the brain of albino rats have been studied⁵⁸ and found to significantly increase the number of lipids and phospholipids in the brain. Rats fed with 1 ml of 5 percent seed oil emulsion for 3-7 days showed improved learning and memory.^{59,60} In another experimental model involving a two-compartment avoidance task, albino rats that were fed

seed oil showed improved cognitive ability compared to saline controls and decreased levels of norepinephrine, dopamine, and serotonin, and their metabolites in the brain and in urine suggesting that these aminergic systems are involved in the memory and learning process.⁶¹ Seed oil 50-400 mg·kg⁻¹ for 14 days was able to prevent amnesic effect of scopolamine in navigational memory performance in rats.⁶² Both the methanol extract of the herb⁶³ and the aqueous extract of the seed^{64,65} showed significant protective effect against free radical damage suggesting that the antioxidant activity may be responsible for its cognitive-enhancing properties and also could offer protection against a host of neurodegenerative diseases. In an animal model of Alzheimer's disease, aqueous extract of *Celastrus paniculatus* was effective in protecting against ICV streptozotocin-caused cognitive impairment.⁶⁶

The seed oil is widely used in psychiatric practice with promising results.⁶⁷ A recent study reported the use of *Celastrus paniculatus* in depressive illness. In a controlled clinical study 55 patients with depression were divided into three groups—group A (24 patients) received two 500 mg tablets of *Jyotishmati* (made from leaves and small stems) thrice daily for 6 weeks, group B (18 patients) received the same dose of *Jyotishmati* in addition to modern treatment (not specified), while group C (13 patients) received placebo. There was statistically significant reduction of symptoms such as sadness, lack of interest, insomnia and psychomotor retardation, and a significant reduction in the degree of depression based on HDRS (Hamilton Depression Rating Scale) in both the treatment groups with respect to placebo, with an additive effect in group B. Similar dropout rates were seen (group A—6, B—4, and C—4).⁶⁸ However, an early double-blind study in mentally deficient patients showed that the seeds had no effect on learning.⁶⁹ In mentally retarded children chronic treatment with *Celastrus paniculatus* oil produced improvement in IQ scores and decreased the content of catecholamine metabolites.⁷⁰

Products from *Celastrus paniculatus* are reported to have low toxicity. However larger doses can cause burning of the skin.⁷¹ In an acute toxicity study the seed oil was given in doses from 0.5 to 5 g·kg⁻¹ body weight to rats. No toxic manifestation, behavioral changes, and mortality were seen even at the highest dose. In a rotorod test, rats given the

seed oil could stay on the rotorod for more than 3 minutes showing no loss of motor coordination. Thus *Celastrus* oil does not have any acute neurotoxic effects.⁶¹

***Convolvulus pluricaulis* Chois. (Family: *Convolvulaceae*)**

Latin: *Convolvulus microphyllus*
Sieb. Ex Spreng, *Convolvulus*
prostratus Forsk

Hindi: Sankahul

Sanskrit: Shankapushpi

Covolvulus pluricaulis is a small, diffuse herb covered with white hairs and bearing white or pale pink flowers from mid-winter to mid-spring found throughout India in the hotter regions.⁷² Like other plants dealt with in this chapter, this plant is also a *medhya rasayana* drug or mental rejuvenator. It was considered by Caraka to be one of the best in this category of mental rejuvenators;⁷³ however, it has not been scientifically investigated to any great degree.

Several alkaloids—convolvine, convolamine, phyllabine, convolidine, confoline, subhirsine, convosine, scopoline, and convolidine have been isolated from the plant, in addition to the ubiquitous sterol— β -sitosterol.⁷⁴ The whole plant is used as the drug.

In small animals, *Convolvulus pluricaulis* has been shown to have tranquilizing activity.^{75,76} The alcoholic extract of the plant and various fractions derived from it have also been shown to have potentiate barbiturate hypnosis^{77, 78} using diazepam as a standard; maximum activity being seen in the water-soluble portion of the chloroform extract⁷⁸ and exhibited by the leaves and flowers,⁷⁹ especially in the spring when the flowering is at its peak.⁸⁰ The activity in the barbiturate hypnosis was better than *Centella asiatica*.⁸¹ The effect of the drug was also tested on the levels of acetylcholine, catecholamine, serotonin, and histamine in normal and stressed rats, and found to act as a tranquilizer, also enhancing cognitive function.⁸² In addition, feeding of *Convolvulus pluricaulis* increased protein synthesis in the hippocampus⁸³ and also influenced GABA levels in the brain tissue and blood.⁸⁴ Furthermore,

the ethanolic extract showed some degree of antioxidant activity, which was not significant.⁸⁵

In an open trial on 30 patients with anxiety neurosis, the drug was given daily in the form of a syrup in 30 ml of divided doses, each dose corresponding to 10 g of crude drug, for a period of 1 month. Patients showed significant symptomatic relief—reduction in anxiety levels, increased work output, decreased stress hormone levels, and lowered blood pressure and pulse rate—apart from a significant reduction in mental fatigue rate after 1 month of therapy.⁸⁶

More scientific work on the chemical, pharmacological, and clinical aspects is required to understand the high esteem in which it was held by Caraka. At this point it may be pertinent to mention that this plant is one of the controversial drugs in Ayurveda and there are discussions as to the identity of this plant, although it has been generally agreed upon by scholars that *Convolvulus pluricaulis* is the accepted source of the drug.

***Withania somnifera* Dunal. (Family: Solanaceae)**

Other aspects of the use of *Withania somnifera* have been covered in Chapter 8, “Antirheumatic agents.” There are several chemotypes of the plant available with varying amounts of the various sitoindosides. The roots have been considered an important mental rejuvenator (*medhya rasayana*) in Ayurveda for 3,000 years, and as being useful in the treatment of various nervous disorders, in improving memory, and being helpful in conditions such as epilepsy and insanity. The drug also helps in the rejuvenation of the nervous system and protects it against environmental influences, improves cognitive deficits due to age, stress, or drugs, and builds nonspecific host defense.⁸⁷

The alcoholic extract of *Withania somnifera* root showed sedative effects in rats, potentiating barbiturate hypnosis, improving learning behavior, and reducing acetylcholine and catecholamine levels, while increasing 5-hydroxytryptamine and histamine levels in the whole brain tissue.⁸⁸ The methanolic extract of *Withania somnifera* showed a GABA mimetic activity.⁸⁹ Defined extracts of *Withania somnifera* consisting of mixtures of Sitoindosides VII-X and Withaferin A prepared by combination of equimolar amounts of the compounds taken from *Withania somnifera* induced an increase in the cortical muscarinic acetylcholine capacity, which may partly explain the cognition-enhancing

effects seen both in animals and humans.⁹⁰ The bioactive withanolides, as a defined mixture described above, administered orally once daily to rats in a dose of 20 and 50 mg·kg⁻¹ for 5 days showed an anxiolytic effect comparable to 0.5 mg·kg⁻¹ lorazepam given intraperitoneally and an antidepressant effect comparable to imipramine (10 mg·kg⁻¹, ip).⁸⁷ This same mixture of sitoindosides and withaferin A when given orally to rats at 20-50 mg·kg⁻¹ in an experimental model of Alzheimer's disease was found at 50 mg·kg⁻¹ to significantly reverse amnesic effect of ibotenic acid and reduce cholinergic markers after 2 weeks of treatment,⁹¹ in addition to demonstrating free-radical scavenging activity and antioxidant activity in chronic footshock-induced stress.⁹² *Withania somnifera* extract at 50, 100, and 200 mg·kg⁻¹ has also been shown to improve retention in a passive avoidance task in a stepdown test, and also shown to significantly reverse amnesic effects of scopolamine (0.3 mg·kg⁻¹). In another experiment, the amnesic effect of electric shock treatment was significantly reversed by daily administration of *Withania somnifera* extract for 6 days.⁹³ Sitoindosides IX and X have been shown in a stepdown test to improve both short- and long-term memory in mice after oral intake.⁹⁴ In addition, the methanol extract of *Withania somnifera* has been shown to promote formation of dendrites in human neuroblastoma cells;⁹⁵ more specifically the axons were extended by withanolide A and dendrites by withanosides IV and VI.⁹⁶ These compound plus a few other similar ones have also displayed significant neurite outgrowth at 1 μM concentration in human neuroblastoma cell line.⁹⁷ In addition, a different extract significantly reduced degenerating cells in the hippocampal region of stressed rats.⁹⁸ Thus, although there is considerable experimental evidence for the possible cognitive-enhancing effects of *Withania somnifera*, there is very little clinical evidence in the form of formal trials, only a single trial in patients of anxiety neurosis is available. However, the drug is extensively used in Ayurveda both as a single drug, and in combination, for various nervous conditions, and needs to be clinically studied.

In an open trial, 30 patients of anxiety neurosis were administered 40 ml of an alcoholic extract of *ashwagandha* in the form known in Ayurveda as *arista*, which is obtained by extraction of the roots of *Withania somnifera* by self-generated alcohol to yield an extract containing 15 percent alcohol; 40 ml of preparation corresponds to 12 g

of dried roots. This preparation was given in divided doses for 1 month and patients were evaluated every week for clinical symptoms such as nervousness, palpitation, tremors, headache, anorexia, insomnia, lack of concentration, dyspepsia, fatigue, and irritability. In addition, various psychological tests were conducted to determine anxiety levels, adjustment level, mental fatigue, and immediate memory span and biochemical determination of stress hormones. After 1 month of treatment there was significant decrease in intensity of symptoms, maximum improvement being seen in nervousness scores. Mental fatigue rate was significantly reduced, assessed in terms of fewer mistakes committed and greater work output after 1 month of treatment. The immediate memory span also increased significantly. Other changes included increased body weight and breath-holding time. In addition, there was reduced urinary excretion of cortisol and catecholamines. There was no change in blood pressure and respiration rate.⁹⁹

In a double-blind placebo-controlled study, the effect of *Withania somnifera* on psychomotor performance of healthy men and women was compared with *Panax ginseng*. Volunteers were divided into three groups. Group 1 received standardized ginseng extract, group 2 volunteers were given 250 mg *Withania somnifera* root powder twice a day for 40 days, and group 3 was given lactose in capsules as placebo. At the end of the treatment period, volunteers on *Withania somnifera* were tested and found to perform better in tasks involving logical thinking, problem solving, and reaction time than the group receiving *Panax ginseng*.¹⁰⁰

Information on the safety of *Withania somnifera* has been covered in Chapter 8, "Antirheumatic drugs."

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PARKINSON'S DISEASE

Parkinson's disease (paralysis agitans) is a degenerative neurological disorder causing muscle tremor, stiffness, weakness, and difficulty with balance and in walking. Paralysis agitans has been described in Ayurveda as *kampavata* (*kampa*, shaking or tremor; *vata* is the principle or humor responsible for all movements). Multiplant preparations containing *Mucuna pruriens* as the source of levodopa are used in Ayurveda for the treatment of *kampavata*.¹

***Mucuna pruriens* Baker (Fl. Br. Ind.) non DC (Family: Fabaceae)**

Latin: <i>Mucuna prurita</i> Hook	Hindi: Kavach
Sanskrit: Atmagupta, Kapikachu	Tamil: Punaikali
English: Common Cowitch, Cowhage	

Mucuna pruriens (see Plate 12 in color gallery) is an herbaceous climber found growing all over India. The pods are covered with highly irritant hairs causing intense itching—the plant is named after this. Inside the pod are 4-6 black seeds, which are used medicinally. The seeds are well known in Ayurveda as an aphrodisiac agent and are also used as an anthelmintic agent, as a nerve tonic, for urinary disorders, and for fertility problems. In times of scarcity, the seeds are also used as food after repeatedly boiling and discarding the resultant liquid.^{2,3}

The seeds contain up to 4-6 percent of L-DOPA – 1-3,4-dihydroxyphenylalanine,^{4,5} about 0.09 percent in the pericarp and 5.28

percent in the endocarp,⁵ glutathione, gallic acid, 0.53 percent alkaloids—nicotine, mucunine, mucunadine, prurienine, prurieninine, and the 5-indoles—tryptamine and 5-hydroxytryptamine, and about 6 percent of a fatty oil.^{2,3}

The clinical study of *Mucuna pruriens* seeds for the treatment of Parkinson's disease⁶ preceded pharmacological studies. Subsequent pharmacological studies in small animals showed that the efficacy of the seed powder against Parkinson's disease was devoid of any cholinergic effect.⁷ The anti-Parkinsonian activity of the seed powder was due not only to the content of L-DOPA but also due to other components,⁸⁻¹⁰ as seen in the activity exhibited in other fractions free from L-DOPA.⁸ Comparison of the CNS profiles of 100 mg·kg⁻¹ of L-DOPA and 3 g of seed powder of *Mucuna pruriens* containing 100 mg of L-DOPA showed similar activity as regards the dopaminergic pathway in showing an equivalent hypothermic and anti-Parkinsonian activity in rats and mice; however, in other aspects seed powder of *Mucuna pruriens* showed a better tolerability and improved anti-Parkinsonian activity due to the presence of other components^{5,10} or adjuvants, which improve the activity of L-DOPA.⁵ In addition, the alcoholic extract of the seeds has potent antioxidant activity.¹¹ The pharmacokinetic profile of a formulation from *Mucuna pruriens* seed known as HP-200 has been studied and found to be similar to formulations of synthetic L-DOPA.¹²

In a trial to assess the efficacy, tolerability, and acceptability of *Mucuna pruriens* in Parkinson's disease patients,⁶ there was a wash-out period of 6 weeks, after which the seed powder was given in a dose of 15-40 g to 23 patients in divided doses, which was gradually increased until patients were receiving about 40-50 g of powder per day for an average treatment period of 20 weeks up to a maximum of 15 g four times a day. Baseline values of the patients compared with the final values showed an overall reduction in the morbidity index. Physical signs and handwriting records showed improvement. The seed powder was well tolerated; however, some patients sought a reduction in bulk. However, this bulk was useful in reducing constipation in patients. Side effects were few—dose dependent and mild—and improved on dose adjustment. These included giddiness, sweating, flatulence, diarrhea of mild nature, and dry mouth and blue-black

urine in one patient of moderate intensity. Bioavailability studies with *Mucuna pruriens* showed significant absorption of L-DOPA from the seed powder.⁶

In another open multicentric study, 60 patients with Parkinson's disease were treated for 12 weeks with HP-200 derived from endocarp of *Mucuna pruriens* to assess its efficacy and tolerability. Twenty-six of the patients had earlier been on synthetic levodopa/carbidopa combination, whereas the remaining 36 were on levodopa alone, which was discontinued before inclusion in the study. The drug prepared from the endocarp of *Mucuna pruriens* was supplied in sachets containing 33.33 mg of levodopa per sachet. Patients were assessed on the United Parkinson's Disease Rating Scale taken before the start of the trial and at the end of 12 weeks. Each patient got an average of 6 ± 3 sachets daily. There was statistically significant improvement in symptoms seen in patients. Side effects were mild, seen infrequently, and were gastrointestinal in nature.¹³

Safety studies carried out on rats and mice have established the product as safe with no abnormalities in blood chemistry, liver and kidney observed, and no gross or histological abnormalities of brain and vital organs.¹⁴ A long-term study, 52 weeks, of the effect of administration of the endocarp of *Mucuna pruriens* to rats found it not to exert any significant alteration on the levels of the monoaminergic neurotransmitters or cause stereotypic behavior.⁹

NOTES

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SEDATIVE PLANTS

Sedative plants are used to calm the mind. “*Svapnajannan*” is the corresponding Ayurvedic category.¹

Nardostachys jatamansi DC (Family: Valerianaceae)

Latin: <i>Nardostachys grandiflora</i> DC	Hindi: Jatamansi, Bal-chir
Sanskrit: Jatamansi	Tamil: Jatamanshi
English: Indian Spikenard, Muskroot, Spikenard	

Nardostachys jatamansi is an erect herb found growing in the Alpine Himalayas at an elevation of 3,000-5,000 m. The rhizome, covered with fine reddish brown fibrous tufts stemming from the leftover

petioles of radical leaves, is used medicinally. The drug is known since the time of Caraka and has been recommended very often by Caraka, Sushruta, and Vāgbhata for nervous disorders, as a sedative, and as a tranquilizer;² however, it has not been much investigated. The rhizome is an official drug in the *Indian Herbal Pharmacopoeia*, 2002, as a sedative.³

The rhizome contains approximately 2 percent of a bitter aromatic essential oil, from which jatamansone has been isolated in 0.02-0.1 percent yields and found identical to valeranone from *Valeriana officinalis*.^{3,40} Other components include a number of sesquiterpenoids such as jatamansic acid, terpenic coumarins, lignans, and neolignans.³

Extracts of the rhizome have shown a sedative effect in small animals.^{5,6} Jatamansone has been shown to have a tranquilizing effect in experimental animals.⁷ Alcoholic extract of the rhizomes cause an overall increase in central monoamines and inhibitory monoamines.⁸ *Nardostachys jatamansi* shows a protective effect in focal ischemia, probably due to its antioxidant activity,⁹ the petroleum ether extract of *Nardostachys jatamansi* having been shown to exhibit a dose-dependent antioxidant property.¹⁰

In an open exploratory study, 24 medical students were given a dose of 60 g of the root powder of *Nardostachys jatamansi* to study its sedative action. There was a prolongation of visual reaction time, the action being observed within an hour of intake, reaching a peak after 3 hours and lasting for 5 hours.¹¹

In a trial on pregnant women, 6 g of *Nardostachys jatamansi* powder was given in two divided doses, and the women were observed in the 25-26th week, 33-34th week, and just before the onset of labor. The trial group women showed reduced anxiety levels and duration of labor, increased baby weight, and an increased crown and rump length in comparison to the control group, who did not receive the medication. The authors conclude that the better growth of the fetus may be due to the anxiolytic effect leading to better uterine circulation.¹²

The LD₅₀ of jatamansone (valeranone) in rats and mice orally was found to be greater than 3,160 mg·kg⁻¹.¹³

Valeriana wallichii DC (Family: Valerianaceae)Latin: *Valeriana jatamansi* Jones

Hindi: Tagar

Sanskrit: Tagara

Tamil: Jatamashi

English: Indian Valerian

Valeriana wallichii is a short, hairy herb found growing in the temperate Himalayas. Caraka describes the use of the rhizome in Ayurveda; however, its use in CNS disorders is mentioned in later books such as the *Dhanvantari Nighantu* and *Bhavaprakash*.¹⁴ In Ayurveda, it is used in delirium, insomnia, epilepsy, and in behavioral disorders.¹⁴ Most of the scientific information with regard to Indian Valerian is in comparison with *Valeriana officinalis*. The rhizomes of *V. wallichii* have a higher percentage of valepotriates: 3-6 percent, as compared to *Valeriana officinalis*: 0.5-2 percent,¹⁵ and therefore classified as a daytime sedative.¹⁶ A review of scientific studies of three *Valeriana* species—*V. officinalis* from Europe, *V. edulis* from Mexico, and *V. wallichii* from India is available.¹⁵

NOTES

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Chapter 13

Rasayana Drugs: Antiaging Agents, Adaptogens, and Immunostimulants

The term *rasayana* in Ayurveda is mentioned way back in the *Caraka Samhita* as an agent that confers long life, youthfulness, freedom from disease, a strong body, maintenance of faculties leading to a gleaming complexion, powerful voice, good eyesight, acuity of mental faculties, and acute hearing—in effect retaining one’s faculties throughout one’s life.¹ With such an enticing prospect, it is little wonder that this concept has aroused great interest in interpreting these outcomes in modern scientific terms.

Studies have shown that some of these effects can be explained in terms of antioxidant activity² protecting the body against free radical damage, stimulation of the immune system, thus protecting the body against infections by increasing host defense,^{3,4} and adaptogenic activity protecting the body against the ill effects of stress, such as environmental conditions.^{3,5} It has also been shown that these *rasayana* plants exhibit organ specificity, as mentioned in Ayurveda.³ For example, there is the whole series of drugs known as *medhya* that are considered to help in enhancing memory, intellect, and retention, covered in Chapter 12. Other herbs such as *Tinospora cordifolia* are recommended for the liver, *Embllica officinalis* for the pancreas, *Asparagus racemosus* for the stomach, and *Piper longum* for the lungs.³

NOTES

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TONIC/ANTIAGING EFFECTS

Among free radical-mediated conditions, aging is also considered to result from free radical damage. According to Caraka, *rasayanas* are drugs that vitalize cells, thereby opening up partially or fully blocked channels (*srotas*). Many of the *rasayanas* have been shown to act as free radical scavengers exhibiting antioxidant activity with the potential to mitigate the effects of aging. Thus, just as antioxidants are taken as dietary supplements, *rasayanas* can be used both for prophylactic and therapeutic use to prevent free radical damage.¹ However, in earlier trials, modern markers of antioxidant activity were not available for evaluation.

***Emblica officinalis* Gaertn. (Family: Euphorbiaceae)**

Latin: <i>Phyllanthus emblica</i> Linn.	Tamil: Nelli
Sanskrit: Amalaki	
Hindi: Amla	English: Indian gooseberry, Embic myrobalan

The fruits of *Emblica officinalis* (see Plate 1 in color gallery) are one of the best-known *rasayana* drugs in Ayurveda, promoting health and youthfulness, protecting the heart and the body, and bestowing, on oral intake, freedom from disease. However, the antiaging, or

rasayana, aspect has not been much investigated in the clinic, with only a few of reports of its usefulness. The fruits are very widely consumed in the form of a confection made out of the fruits and several other herbs and taken as a multiherbal preparation known as *Chyavan-prash* named after the sage Chyavan, who used it for rejuvenation. In order to make it available at home throughout the year the fruit is made into jam, pickles, the whole fruit preserved in honey, or its pieces sun-dried to add, when required, into food items.

Aging has been considered to result from free radical damage, and agents displaying the antioxidant effect protect the body and mind from aging. Fruits of *Embllica officinalis* exhibit a potent antioxidant effect,^{2,3} which was first attributed to the high content of Vitamin C (600-900 mg per 10 g of fresh fruit).⁴ Later experiments have suggested that the fruits are devoid of Vitamin C.⁵ The antioxidant activity has been postulated to arise from the tannins emblicanin A and B, punigluconin, and pedunculagin,⁶ which have been shown to protect the heart⁷ and the brain⁸ from oxidative stress, rather than Vitamin C. The aqueous extract of *Embllica officinalis* exhibits an adaptogenic effect and protects experimental animals from a variety of stresses—physical, chemical, and biological,⁹ whereas the fresh fruit homogenate on chronic administration protected the heart against oxidative stress.¹⁰ Flavonoids from *Embllica officinalis*, apart from their potent hypolipidemic and hypoglycemic effects, also improve the blood picture by raising hemoglobin levels.¹¹

Thus, there is evidence from experimental studies that the fruits are potent antioxidants, with favorable effects on several organ systems; however, evidence from clinical trials is scanty. In an early experimental study in rabbits, there was improvement in body weight and total serum protein content.¹²

In studies carried out at Varanasi, the preparation obtained from fruits of *Embllica officinalis* triturated 21 times with the fresh juice of the fruit and then dried and powdered, which is known as *Amalaki rasayan*. There was increase in body weight in clinical cases, positive nitrogen balance, increased serum mucopolysaccharides, and a decreased excretion of hydroxyproline indicating greater turnover, repair, and regeneration of connective tissues.¹³

In another study, patients undergoing surgery for inguinal hernia and senile enlargement of prostate in the age group of 55-60 years were given 10 g of *Amalaki rasayan* in three divided doses for 10 days prior to surgery. Treatment was evaluated on the basis of time taken for ambulation, early return of physiological functions such as passage of flatus, and changes in serum mucopolysaccharides, hydroxyproline, urinary nitrogen, blood picture, and blood sugar levels against the time taken by patients maintained as control. Patients treated with *Amalaki rasayan* did not show any loss of body weight, had improved hematological picture, were ambulatory earlier, and had early return of physiological functions. In addition, biochemical parameters also indicated a favorable return of connective tissue turnover.¹⁴ The safety of *Emblica officinalis* is covered in Chapter 3, "Gastrointestinal agents."

This promising fruit needs to be further studied.

***Withania somnifera* Dunal. (Family: Solanaceae)**

Withania somnifera has been covered in Chapter 8, "Antirheumatic agents" and in Chapter 12 "Central nervous system agents." The roots are considered to have a health-promoting effect, improving stamina, warding off disease, and toning up the body and mind. In a double-blind placebo-controlled trial, *Withania somnifera* has been shown to improve the health of adult volunteers over a period of 1 year. It has also been used in children to improve health.

Studies in small animals have shown that *Withania somnifera* exerts an adaptogenic effect against a variety of physical¹⁵⁻¹⁷ biological,¹⁶ and chemical stressors,¹⁶ and in a chronic stress model.¹⁸ There was significant increase in the physical working capacity and an increase in the heart weight and glycogen content of the myocardium and liver.¹⁷ Adaptogenic activity has also been shown in a withanolide-free fraction from *Withania somnifera*.^{19,20} The aqueous suspension²¹ and the methanolic extract²² of *Withania somnifera* and the glycowithanolides^{23,24} consisting of equimolar concentrations of sitoindosides VII-X and withaferin A have been shown to exhibit antioxidant activity. *Withania somnifera* has also been shown to exhibit immunostimulatory activity with significant increase in hemoglobin concentration, red blood cell count, white blood cell count, platelet count, and

body weight as compared to untreated control in different animal models of myelosuppression.²⁵ Increased synthesis of nitric oxide by macrophages has been postulated to partly explain the immunostimulatory activity of *Withania somnifera*.²⁶

In a double-blind placebo-controlled clinical trial to study the effect of *Withania somnifera* on normal healthy male volunteers in the age group 50-59 years, powdered root of *Withania somnifera* made into 500 mg tablets or a similar tablets made of starch, which was matched as far as possible for color, strength, and appearance, was given. A total of 331 volunteers were screened and 141 subjects, who did not have diseases such as diabetes, asthma, CHD, hypertension etc. were included in the trial and randomly allocated to receive the drug or placebo, two tablets thrice daily with milk for 1 year; 101 volunteers completed the treatment. There was significant increase in hemoglobin and red blood corpuscles in the treated group. Other significant changes included an increase in seated stature, increase in hair melanin content, reduced decrease in nail calcium, greater decrease in serum cholesterol, and erythrocyte sedimentation rate in the treated group as compared to placebo. Approximately 71 percent of volunteers reported subjective improvement in sexual performance. No side effects were seen.²⁷

In another double-blind study conducted on normal male and female children, ages 8-12 years, the effect of *Withania somnifera* was compared with *Withania somnifera* and *Boerhaavia diffusa*, ferrous fumarate at two different concentrations and placebo in different groups along with milk for 60 days. Thus, group 1 received 2 g·day⁻¹ of *Withania somnifera*, group 2 received 2 g of a 1:1 mixture of *Withania somnifera* and *Boerhaavia diffusa*, group 3 received 2 g lactose mixed with 5 mg of ferrous fumarate, group 4 received 2 g lactose mixed with 30 mg of ferrous fumarate, whereas group 5 received 2 g lactose powder, all medications with 100 ml of milk. All the children received similar diet and had similar environmental conditions since they were inmates of a local orphanage. Baseline values were estimated before the start of the trial. It was found that there was increase in body weight and a significant increase in mean corpuscular hemoglobin and total protein over the initial level in group 1 on *ashwagandha*, in comparison to placebo. In group 2, receiving a 1:1

mixture of *ashwagandha* and *punarnava*, although there was increase over initial values in several parameters such as hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, serum iron, and hand grip, only hemoglobin and hand grip differed significantly from placebo. In children in group 4 receiving 5 mg ferrous fumarate and those in group 5 receiving placebo, there was no significant change in any of the parameters studied, whereas in group 3 receiving 30 mg ferrous fumarate, there was significant increase in hemoglobin, corpuscular hemoglobin, serum iron, and in hand grip compared to the placebo group. The results in group 1 and 2 led the authors to recommend fortifying milk with the *Withania somnifera* and *Boerhaavia diffusa* to improve growth and strength in growing children and increasing the quantity of *Withania somnifera* in the combination in order to take advantage of the hematinic properties of *Withania somnifera*, pointing out that the quantity of iron in *ashwagandha* is equal to that in 5 mg of ferrous fumarate.²⁸

In another study, *Withania somnifera* and *Tinospora cordifolia* were administered to separate groups of patients for 3 months to study potential antiaging effects, better results were achieved with *Tinospora cordifolia*. However, this study has been published in the form of an abstract and hence further details are not available.²⁹

Considering the importance of the results obtained and the advances in analytical methodology it is worthwhile laying down the specifications for the material to be used, which are then followed by further trials with larger numbers of volunteers to confirm the results obtained in these studies. Aspects of the safety of *Withania somnifera* have been dealt with in Chapter 8, "Antirheumatic agents."

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OTHER TONIC/ANTIAGING PLANTS

***Centella asiatica* (Linn.) Urban. (Family: Apiaceae)**

Latin: *Hydrocotyle asiatica* Linn.

Tamil: Vallarai

Sanskrit: Mandukaparni

English: Indian Pennywort

Hindi: Brahma Manduki

In a double-blind clinical trial carried out on 43 normal adults divided into two groups using either *Centella asiatica* (see Plate 8 in the color gallery) or *Boerhaavia diffusa* for 1 year, patients were evaluated at 6 months and 1 year. In the *Centella asiatica* group, there was a significant improvement in the number of red blood corpuscles, vital capacity, and total protein. There was also a significant improvement in hemoglobin levels with a decrease in blood urea and serum acid phosphatase.^{1,2}

NOTES

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IMMUNOSTIMULANT EFFECTS AGAINST INFECTION

Plants used as *rasayanas* have the potential to promote health by strengthening host defense against different diseases rather than specific action on the disease. This can be seen in the examples that follow and also in Chapter 4 where *Tinospora cordifolia* was used as an adjuvant to antibiotics following surgery for obstructive jaundice.¹

***Tinospora cordifolia* Miers. (Family: Menispermaceae)**

Latin: <i>Tinospora glabra</i> (N.Brums.) Merr	Hindi: Giloe
Sanskrit: Guduchi, Amrita	Tamil: Sindal

The use of *Tinospora cordifolia* (see Plate 4 in color gallery) in obstructive jaundice has been covered in section, "Hepatoprotective agents" in Chapter 4 and also as an anti-inflammatory agent in Chapter 8, "Antirheumatic agents." There has been a considerable amount of work on the immunomodulatory activity of the plant, several immunostimulating compounds having been isolated. Syringin and cordiol show anticomplementary activity, increase IgG antibodies, and increase humoral and cell-mediated immunity in a dose-dependent manner. Cordioside, cordifolioside A, and cordiol show macrophage activation.² An immunologically active arabinogalactan was isolated from *Tinospora cordifolia*³ and shown to possess antioxidant activity⁴ and an inhibitory effect on experimental metastasis.⁵

Tuberculosis

Tinospora cordifolia is considered a *rasayana*, which protects against infection. It has been shown in a series of experiments upon small animals to be a powerful immunostimulant, which increases host defense both in normal and in immunocompromised states¹ through activation of the immune cells such as the macrophages, and especially the peritoneal and alveolar macrophages.⁶ The modulation of the alveolar macrophage function in rats by *Tinospora cordifolia* has been studied both by itself and in combination with modern anti-tubercular (anti-TB) drugs and then compared with that produced by standard anti-tubercular drugs.⁷ The studies have shown that the phagocytic and intracellular killing capacity of the alveolar macrophages has been increased through stimulation of nitric oxide (NO) synthesis in alveolar macrophages by *Tinospora cordifolia*, whereas it is significantly reduced by anti-TB drugs. When *Tinospora cordifolia* was coadministered with anti-TB drugs the decrease of NO production was prevented.⁸

In a double-blind placebo-controlled trial the effect of coadministration of either 500 mg thrice daily of *Tinospora cordifolia* or placebo along with standard anti-TB drugs was evaluated in 31 patients, and these patients were assessed early on in the first 2 months of treatment. At the end of 2 months, the data available for 20 patients shows that addition of *Tinospora cordifolia* produced a number of useful effects and lowered composite clinical score faster than placebo. The patients gained weight, had reduced sputum conversion time, had improved radiological picture, and had an improved quality of life with fewer side effects and dropouts.⁸ The effect of coadministration of *Tinospora cordifolia* (500 mg thrice a day) against placebo was also evaluated in TB patients on a short-term anti-TB regime for 6 months, and in a larger number of patients (24 on *Tinospora cordifolia* and 22 on placebo) confirmed results obtained earlier. At 6 months there was no significant difference between placebo and *Tinospora cordifolia*. There were fewer adverse effects reported and fewer dropouts in the *Tinospora cordifolia* group.⁹

Thus, adding *Tinospora cordifolia* (TC) to anti-TB drugs seems to hasten recovery and improve quality of life at the end of 2 months;

however, at the end of 6 months the differences seem to have evened out.^{8,9} Thus in a double-blind placebo-controlled study with 50 patients—23 on TC and 27 on placebo—47 percent of the placebo group showed improvement, whereas 75 percent of the TC group showed progress including radiological improvement. In addition, there were fewer side effects in the TC-treated group (15 percent) as compared to placebo (40 percent) at the end of 2 months.⁶

Asthma

In ten chronic asthmatics treated with one 500 mg tablet of *Tinospora cordifolia* aqueous extract thrice daily for 8 weeks there was considerable improvement in the quality of life, reduced frequency of asthmatic attacks, and decrease in severity of symptoms, such as coughing and wheezing.¹⁰

The safety of *Tinospora cordifolia* is covered in Chapter 4, “Hepatoprotective agents.”

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OTHER IMMUNOSTIMULANT PLANTS

See also Chapter 5, “Respiratory tract drugs” section “Upper-respiratory tract infections.”

***Centella asiatica* Urban (Linn.) (Family: Apiaceae)**

Centella asiatica (see Plate 8 in color gallery) is a small creeping herb found growing throughout India near water bodies. It is traditionally used in Ayurveda for a number of conditions including cough, bronchitis, and asthma,¹ and is considered an antiaging herb that fortifies the immune system.² See also Chapters 6, 9, and 12.

The alcoholic extract of *Centella asiatica* has been shown to have a stimulatory effect on the reticuloendothelial system in mice.³ In addition, the aqueous extract has been shown to have a positive effect on the complement system.⁴ Rats fed orally with 100 mg·kg⁻¹ body weight per day of aqueous suspension of *Centella asiatica* for 7 days showed an immunostimulant activity, which was assessed to be comparable to 60 percent that of interferon alpha2b.⁵

Treatment for 1 month of aged persons with *Centella asiatica* was found to give significant relief in common ailments, such as cold, cough, and bronchitis. There was significant increase in serum IgM ($p < 0.01$) and IgG ($p < 0.05$) levels indicating a general increase in immunity.⁶

The safety of *Centella asiatica* is covered in Chapter 6, “Cardiovascular drugs” and in Chapter 12, “Central nervous system agents.”

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CANCER THERAPY

Cancer is a malignant growth, or tumor, formed by abnormal, rapid reproduction of cells. In Ayurveda, a number of predisposing factors have been enunciated as a result of which a tumor can develop—imbalance in the humors (*doshas*), poor digestion, and absorption leading to formation of undigested food particles, deposition in the tissues, and enzyme malfunction that result in a tumor development.¹ From a list of 100 plants used traditionally for the treatment of cancer, 44 have been postulated as having anticancer activity. Other authors have arrived at similar figures of active plants.^{2,3} Although there has been substantial pharmacological work, the clinical work is miniscule and mostly as adjuvants to modern therapy.

***Boswellia serrata* Roxb. ex Coleb** (Family: *Burseraceae*)

Boswellia serrata (see Plate 2 in color gallery) resin has been covered in Chapter 3, "Gastrointestinal agents," in Chapter 5, "Respiratory tract drugs," and in Chapter 8, "Antirheumatic agents," where its use as an anti-inflammatory agent has been covered in a variety of conditions where leukotrienes play a key role in causation and in the persistence of the disease. Traditionally, the gum is reported to be useful in ulcers, tumors, goiter, cystic breast, diarrhea, dysentery, piles, and skin dis-

eases.⁴ The nonphenolic portion of the gum resin has been reported to possess antitumor, analgesic, and sedative activity.⁴

The 50-percent alcoholic extract of the root, fruit, and stem showed anticancer activity against several cancer screens—human epidermal carcinoma of the nasopharynx in tissue culture, lymphoid leukemia, sarcoma 180, and hepatoma 129 in mice.⁵ In mice transplanted with Ehrlich ascites carcinoma and S-180 transplantable tumors, it increased longevity of mice with ascites by 24 percent and reduced tumor size of S-180 tumors by 24 percent.⁶ Recent in vitro studies using human cell culture lines have also shown that the resin and the boswellic acids derived from it show anticancer activity against various cancers, notably against leukemia and brain tumors,⁷ also in colon cancer cells⁸ and in liver cancer HepG2 cells,⁹ due to induction of cell death and modulation of enzyme activity.⁷⁻¹⁰ In addition, the boswellic acids showed anticancer activity when applied topically against skin cancer in mice.¹¹

Boswellic acids^{10,12} such as 3-O-acetyl-11-keto- β -boswellic acid and 3-O-acetyl- β -boswellic acid, and β -boswellic acid have been shown to be cytotoxic to human glioma cell lines, at inhibitory concentrations (IC_{50}) ranging from 20 to 40 μ M.¹² In rats with induced tumors receiving different dosages of the gum resin extract, those receiving the highest dosage (3×240 mg·kg⁻¹ body weight) had twice the survival time of untreated controls ($p < 0.05$) with significantly larger number of apoptotic tumor cells.¹³ Acetyl boswellic acids have been shown to be catalytic inhibitors of both topoisomerase I and II simultaneously, which could result in enhanced antitumor efficacy.¹⁴ *Boswellia serrata* extract has been shown to be more potent than pure 3-O-acetyl-11-keto- β -boswellic acid in three hematological cell lines.¹⁵ Acetyl-11-keto- β -boswellic acid showed a potent cytotoxic activity against meningioma cells (IC_{50} 2-8 μ M), mediated partly by inhibition of the Erk signal transduction pathway that plays an essential role in signal transduction and tumorigenesis¹⁶ by interfering/interrupting with the signals that play an important role in cell proliferation and cell death of different tumors.

Clinical studies carried out on peritumoral edema in brain tumors, such as astrocytoma and glioblastoma using much larger doses than earlier used for the treatment of arthritis, bronchial asthma, and in-

inflammatory bowel diseases, have shown a reduction in the edema, but not of the tumor itself, perhaps due to the short treatment periods employed. It was earlier thought that there was increased formation of leukotrienes when such tumors are present.

In an open study in patients with malignant astrocytomas, there was an increased excretion of leukotrienes E_4 (LTE_4), which decreased after surgical intervention but returned to higher values when there was a relapse. Treatment with three 400 mg *Boswellia serrata* extract tablets administered thrice a day to patients for 7 days showed again a decrease in the levels of LTE_4 in the urine.¹⁷

In an exploratory controlled study with 29 patients with malignant glioblastoma, 14 patients received 1,200 mg of *Boswellia serrata* extract (H15) thrice daily, 9 patients received 800 mg thrice daily, and 5 patients 400 mg thrice daily 7 days before operation. Only patients receiving the highest dose had significant reduction of the perifocal edema volume, not in tumor size after 7 days intake.¹⁸

In another study on 12 patients with brain tumor and progressive edema, treated with 1,200 mg of *Boswellia serrata* extract (H15) for several months, two out of seven patients with glioblastoma and progressive tumors and three out of five patients with treatment-related leukoencephalopathy showed reduction in the perifocal edema volume. All patients of leukoencephalopathy showed improvement in clinical symptoms for many months.¹⁹

In another study, 19 children and adolescents with intracranial tumors received palliative therapy with H15 for a median period of 9 months with a maximum dose of $126 \text{ mg} \cdot \text{kg}^{-1}$ body weight. All the patients had earlier been treated by conventional therapy. A total of 5 out of 19 patients improved in general health, 3 out of 17 patients with malignant tumors showed a transient improvement in neurological symptoms, 3 patients showed improved muscle strength, whereas 1 cachectic patient gained weight, possibly due to the antiedematous effect of *Boswellia serrata* extract.²⁰

In the glioblastoma trial¹⁸ with increased dosages up to 1,200 mg thrice daily some patients complained of nausea and vomiting and two patients of skin irritation, which was reversible on stoppage. However, side effects were also not seen at 1,200 mg.¹⁹ In the trial with children no side effects were seen when they received a maxi-

mum dose of 126 mg·kg⁻¹ bodyweight.²⁰ See also Chapter 3, “Gastrointestinal agents” and Chapter 5, “Respiratory tract drugs.”

***Cucuma longa* Linn. (Family: Zingiberaceae)**

Curcuma longa and the pigment curcumin derived from it have been extensively investigated and they display a range of useful effects. *Curcuma longa* has been covered in Chapter 3, “Gastrointestinal agents” for use in dyspepsia, in Chapter 5, “Respiratory tract drugs” for use in asthma, and in Chapter 8, “Antirheumatic agents” for use in rheumatoid arthritis. Both the crude drug extract and curcumin are powerful antioxidants^{21,22} and exhibit anti-inflammatory effects.²³

Curcuma longa is not classified as a *rasayana*. Turmeric and curcumin display considerable potential both for the treatment and prevention of cancer in a variety of cancers and they have been extensively investigated for their anticancer effects in vitro and in experimental animals, which have been reviewed.²⁴⁻²⁷ Curcumin acts on a variety of tumors by suppressing proliferation,²⁸ through down-regulation of transcription factors,²⁹ down-regulation of the expression of a number of chemokines such as COX-2, lipoxxygenase, NO synthase, Tumor Necrosis Factor etc., cell-surface adhesion molecules, and certain growth factors, apart from inhibition of certain kinases, which have been reviewed.²⁷

In an open study carried out on 111 patients, of whom the data from 62 patients with external cancerous lesions could be evaluated, both an ethanol extract of *Curcuma longa* containing 0.5 percent curcumin and an ointment containing 0.5 percent curcumin in white Vaseline applied thrice daily gave patients considerable symptomatic relief, which was considered remarkable by the authors. A reduction in smell was noted in 90 percent cases and a reduction in itching in nearly all cases. Although 10 percent patients experienced a reduction in lesion size and pain, 70 percent of patients had dry lesions. The effects of the drug continued for several months in many of the patients. An adverse reaction was noticed only in 1 patient who complained of itching from the 62 patients treated in the study.³⁰

In another study carried out on 16 chronic smokers whose urine showed positive for mutagens with Ames’s test, treatment with 1.5 g

of *Curcuma longa* for 4 weeks showed significant reduction in the mutagenic response in comparison to controls consisting of 6 non-smokers.³¹

Oral submucous fibrosis is commonly observed in India as a result of chewing betel nut containing masticants and their exfoliated oral mucosal cells contain significantly larger number of micronucleated cells when compared to healthy subjects not indulging in chewing or smoking.³² In a trial on patients with submucous fibrosis, three treatment modalities were tried out after initial in vitro tests, on the effect of alcoholic extract of turmeric, turmeric oil, and turmeric oleoresin, were shown to protect against benzo[a]pyrene-induced increase in micronuclei in circulating lymphocytes, whereas they did not cause any increase in the number of micronuclei in lymphocytes taken from normal healthy subjects when compared to untreated controls. Patients with submucous fibrosis were treated with a total oral dose per day of 600 mg turmeric oil mixed with 3 g of alcoholic turmeric extract. Turmeric oleoresin 600 mg plus 3 g turmeric extract and 3 g turmeric extract per day served as controls. All the three treatment arms reduced the number of micronucleated cells both in the exfoliated oral mucosal cells and in circulating lymphocytes. Turmeric oleoresin was found to be more effective than the others in reducing the number of micronuclei in oral mucosal cells, although in circulating lymphocytes the decrease in micronuclei were comparable in all three groups.³³

Curcumin

A phase I clinical trial has been carried out on 25 patients having high risk or precancerous lesions in order to check dose response and safety profile. Patients who received up to 8 g·day⁻¹ of curcumin for 3 months showed no signs of toxicity. Although the study was designed to assess safety of the drug, there were preliminary therapeutic results with one out of two patients with recently resected bladder cancer, two out of seven patients of oral leukoplakia, one out of six patients of intestinal metaplasia of stomach, one out of four patients with cervical intraepithelial neoplasm (CIN), and two out of six patients with

Bowen's disease of the skin showed histological improvement of pre-cancerous lesions.³⁴

In another phase I clinical trial on patients with advanced colorectal cancer refractory to standard treatment received an alcoholic extract of *Curcuma longa* in doses from 440 to 2,200 mg per day of extract for 4 months corresponding to 36-180 mg of curcumin, which was well tolerated. These dosages were considered safe and serve as reference dosages for further studies.³⁵

Other aspects of the safety of *Curcuma longa* and curcumin are covered in Chapter 3.

***Tinospora cordifolia* Miers.**
(Family: *Menispermaceae*)

Tinospora cordifolia (see Plate 4 in color gallery) has been mentioned earlier in this chapter for the treatment of tuberculosis and improving the quality of life in chronic asthmatics. Several compounds have been shown to have immunostimulating properties as discussed earlier in this chapter, the polysaccharide fraction has been shown to be effective in reducing experimental metastasis in mice.³⁶ The immunostimulating activity of *Tinospora cordifolia* is comparable to lithium carbonate and glucan.³⁷ Activation of macrophages by *Tinospora cordifolia* leads to an increase of colony-forming units of granulocyte macrophages, which again leads to leukocytosis and improved neutrophil function.³⁸ When the carcinogen ochratoxin A was administered to mice, *Tinospora cordifolia* was able to inhibit suppression of chemotactic activity and the production of interleukin-1 and Tumor Necrosis Factor-alpha, which is a sign of increased cancer activity.³⁹ In Dalton's lymphoma *Tinospora cordifolia* alcoholic extract showed antitumor activity by activating tumor-associated macrophages. The extract given intraperitoneally slowed down tumor growth and increased life span of the host.⁴⁰ Administration of the methanol extract of the *Tinospora cordifolia* stem in experimental animals increased total white blood cell count, increased bone marrow cellularity, increased the humoral immune response, and reduced tumor volume by 58.8 percent, and acted synergistically with cyclophosphamide in reducing animal tumors by 83 percent.⁴¹ Flow

cytometric measurements in mice showed that *Tinospora cordifolia* induces a dose-dependent increase in bone marrow proliferation.⁴² In vitro the methanol, water, and methylene chloride extracts of *Tinospora cordifolia* caused a significant, dose-dependent increase in cell death,⁴³ and also enhanced the effect of radiation in cultured HeLa cells.⁴⁴ A dose-searching study on humans showed that *Tinospora cordifolia* has great potential in reducing neutropenia caused by cytotoxic drugs in patients with cancer.⁴⁵ In small animals it is also able to reduce toxicity of cyclophosphamide.⁴⁶

In a double-blind placebo-controlled randomized study, 40 patients with breast cancer were treated with tablets of 500 mg *Tinospora cordifolia* aqueous extract thrice daily as an adjuvant in cancer chemotherapy using the combination of methotrexate, 5-fluorouracil, and cyclophosphamide. In the group receiving *Tinospora*, the number of patients whose peripheral blood counts fell below 3,000/cu.mm was 55 percent compared to 70 percent in the placebo group. In the placebo-treated group the level fell below 2,000/cu.mm 24 times as compared to 14 times in the *Tinospora* group, and below 500/cu.mm 5 times in the placebo group as compared to only once in the *Tinospora* group.⁴⁷

In another study in 26 patients with breast cancer, use of 500 mg *Tinospora cordifolia* standardized aqueous extract thrice daily in addition to chemotherapy resulted in fewer adverse reactions in the *Tinospora* group. *Tinospora cordifolia* also increased the apoptotic index in a dose-dependent manner in 4,937 cells, apart from synergistically increasing apoptosis induced by methotrexate, cytarabine, and cisplatin.⁴⁸ These findings led the authors to conclude that *Tinospora cordifolia* shows promise as an adjuvant in cancer chemotherapy.⁴⁸

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OTHER PLANTS USED IN CANCER THERAPY

Withania somnifera Dunal. (Family: Solanaceae)

Withania somnifera has been extensively screened for possible use in cancer chemotherapy and for radio-sensitization, which have been reviewed.¹ Pilot studies in patients with advanced oral cancer indicates that it may be of use when administered alongside conventional radiotherapy. No side effects were observed and blood GSH levels showed a reduction.¹ Six patients were given 400 mg of alcoholic extract of *Withania somnifera* daily along with radiotherapy. The tu-

mors disappeared in three patients and the response of the remaining three patients was considered good.²

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Chapter 14

Dental and Ophthalmological Agents

DENTAL HEALTH

Plaque formation and subsequent chronic inflammation are the major cause of problems connected with teeth and gums. Plaque is the sticky coating formed on the surface of the teeth with saliva and food debris by several bacteria, including the bacterium *Streptococcus mutans* after consumption of food. If plaque is not removed, it gets converted to tartar by deposition of the calcium salts of the saliva. Further progression by attack of the acids produced by the bacteria in the plaque can lead not only to tooth decay or caries but also to inflammation of the gums or gingiva (gingivitis). Prolonged inflammation leads to loosening of the teeth and the condition known as periodontitis.¹ In addition, the importance of maintaining the health of the oral cavity has been brought out by establishing the connection between chronic low grade inflammation and heart disease.²

Thus preventive care of teeth by preventing plaque formation is very important for maintaining the health of the oral cavity, and in Ayurveda dental care was carried out at three levels—prophylaxis in the form of daily care as part of the daily routine or *dinacharya*, treatment of minor conditions by drugs, and surgical interventions for serious conditions.³

In Ayurveda, plants play an important role in the maintenance of healthy teeth and gums and these are generally used in combination. Some 84 plants have been used for this purpose—as chewing sticks, as tooth powder for cleaning teeth and gums, for pyorrhea, for sensitive teeth, gum inflammation, toothache, and caries, which have been

reviewed.⁴ The herbs that were most commonly used were also the ones that were readily available such as *Azadirachta indica*, *Mangifera indica*, *Ocimum sanctum*, *Camellia sinensis*, and curry leaf *Murraya koenigi*.⁵ However, only a few of them have been scientifically investigated.

***Azadirachta indica* Linn. (Family: Meliaceae)**

Azadirachta indica has been covered in Chapter 9, “Dermatological agents” and in Chapter 11, “Antidiabetic agents.” The use of *neem* twigs as chewing sticks for brushing the teeth has been known in India for a very long time. People brushing their teeth with twigs of *neem* is even today a common sight on Indian roadsides, where a twig of *neem* is selected with great care, one end chewed and softened with a stone in order to obtain a soft surface, which is used to clean the teeth and gums. Toothpastes incorporated with *neem* extracts are available in the market in India. Various parts of the *neem* tree have shown antibacterial properties, which have been summarized.⁶ Aqueous extract derived from sticks of *neem* was tested against *Streptococcus mutans* and *Streptococcus faecalis* and found active at 50 percent concentration.⁷ Aqueous extract from bark-containing sticks of *Azadirachta indica* have also been shown to reduce the ability of some oral *Streptococci* to colonize tooth surfaces.⁸

In an exploratory study, extracts derived from plants such as *neem*, *tulasi* (*Ocimum sanctum*), walnut, and acacia have been used to treat plaque, periodontitis, and gingivitis in order to assess their efficacy. In the plaque-control study, the plant extracts were used for 3 days and then the plaque that was still left was scored using Quigley and Hein scoring method. A 1 percent *neem* extract was found to inhibit plaque formation by 80 percent. In the gingivitis study, a 1 percent solution of nimbidin-T reduced gingivitis by 12 percent after two applications, but maximal reduction of 70 percent reduction was seen only after 45 days. In a microbiological study, a 6 percent *neem* leaf extract eliminated aerobic organisms by the 4th day and anaerobic microorganisms on the 5th day.⁹

In another exploratory study, the antibacterial effect of *neem* mouthwash on the levels of *Streptococcus mutans* and *Lactobacillus*

was assessed in the saliva for a period of 2 months. In addition, the effect on incipient carious lesions was evaluated. A total of 150 schoolchildren between the ages of 9 and 12 were selected and divided into five groups out of which three groups were test groups, one group was positive control, and one group received placebo. Out of the three treatment groups, two groups received 3 percent *neem* mouthwash with base, one with alcohol and the other without alcohol, group 3 received chlorhexidine, group 4 received base alone, whereas group 5 was on oral prophylaxis. Thus *Streptococcus mutans* was inhibited in both groups 1 and 2 using *neem* mouthwash, but not *Lactobacillus*, which was inhibited only by chlorhexidine. In addition, there is evidence from initial data that there is a reversal of incipient carious lesions, therefore, there is a need to conduct longer duration trials to confirm the initial results.¹⁰

In a study involving 36 subjects divided into three groups, the efficacy of a dental gel prepared from 70 percent alcoholic extract of *neem* leaf was evaluated against 0.2 percent chlorhexidine gluconate solution and against placebo gel. Subjects used the preparations twice a day for 6 weeks. Microbial evaluation of *Streptococcus mutans* and *Lactobacillus* species was carried out to determine the change in bacterial count over the treatment period. There was significant reduction in the plaque index and bacterial count in the group using *neem* extract gel over the control group using chlorhexidine gluconate mouthwash.¹¹

The use of *neem* chewing sticks and neem toothpastes is widespread and no side effects or toxicity have been reported.

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OTHER DENTAL CONDITIONS

Pyorrhea

Pyorrhea is the chronic destructive inflammation of the tissues surrounding the teeth (periodontium) characterized by bleeding, pus, and bad breath. If pyorrhea is not controlled it can lead to loss of teeth.

***Adhatoda vasica* Nees (Family: *Acanthaceae*)**

Latin: <i>Adhatoda zeylanica</i> Medicus, <i>Justicia adhatoda</i> Linn.	Hindi: Arusa
Sanskrit: Vasa	Tamil: Adhatodai
English: Malabar Nut Tree	

Adhatoda vasica has been covered in Chapter 3, “Gastrointestinal agents” and in Chapter 5, “Respiratory tract drugs.” The leaves have been used to lessen gingival inflammation. In an open trial, 25

patients with pyorrhea, bleeding gums, and pus discharge were asked to apply *Adhatoda vasica* leaf extract on the gums for 3 weeks. The herb extract was prepared by mixing two parts of crushed leaves of the plant with one part of honey and applied twice a day on the gums. The gingival inflammation (GI) index was examined once a week for 3 weeks. Most of the patients had a gingival score of 2-2.5 indicating an advanced state of inflammation, with the mean score being 1.9. The scores came down to 1.7, 1.5, and 1.3 every week showing significant reduction in all the 3 weeks offering great relief to the patients, with reduction in bleeding, pus, and halitosis.¹ Further studies are warranted in larger patient numbers in view of the promising results.

Local Anaesthetic

Anacyclus pyrethrum DC (Family: Asteraceae)

Latin: *Anacyclus officinarum* Hayne

Hindi: Akarkara

Sanskrit: Akaraakarabha

Tamil: Akkirakaram

English: Spanish Pellitory

Anacyclus pyrethrum is a perennial, procumbent herb native to North Africa and cultivated on an experimental scale in Jammu and Kashmir. The roots have since long been imported into India for use in medicine. The root is used to provide relief from toothache.² The roots contain anacyclin—an acetylenic compound—pellitorine—the intensely pungent active principle that is a mixture of isobutylamides, although it is uncertain if it contributes to the analgesic activity—enetriyne alcohol, hydrocarolin, about 50 percent inulin, volatile oil, sesamin, and some tyramine amides.² In experimental animals the root extract has been shown to have local anesthetic activity.³

In a double-blind study on 200 patients undergoing oral surgery the anesthetic effect of a 2 percent alcoholic extract of *Anacyclus pyrethrum* root freshly dissolved in sterile water was compared with xylocaine. The effect on surgery, postoperative recovery, and rate of wound healing were also evaluated. The extract had a longer period

of anesthesia when compared to xylocaine and therefore found to be useful in prolonged oral reconstructive surgery.⁴ The drug was evaluated as safe.⁴ The LD₅₀ of the aqueous extract of the root was 750 mg·kg⁻¹ in mice given intraperitoneally.⁵

Periodontitis

Chronic inflammation of the tissues surrounding the teeth (periodontium) leads to loosening of teeth and eventually to tooth loss. In Ayurveda, the periodontium is described as *dantamula* and periodontal diseases as *dantamulagataroga*.

Triphala

Triphala (*tri*: three; *phala*: fruits) is the well-known three-fruit combination of equal parts of *Terminalia chebula*, *Terminalia bellerica*, and *Embllica officinalis*, which is commonly used in Ayurveda as a bowel tonic, in oral health care, and for the care of the eyes. *Triphala* has shown significant analgesic, antiarthritic, and anti-inflammatory activity.⁶ When tested for putative use in pyorrhea against 22 species of bacteria, *triphala* decoction was active inhibiting growth of 16 bacteria.⁷

In a controlled study, 60 patients in different stages of inflammatory periodontal disease were selected on the basis of clinical symptoms and diagnostic criteria and divided into three groups of 20 patients each. Group I patients were treated with *triphala* decoction as mouthwash and given 3 g *triphala* powder twice daily for 1 month. Group II was the control group patients who were treated with 400 mg metronidazole thrice daily for 7 days together with *triphala* decoction as mouthwash twice daily for 1 month. Group III of 20 patients again served as control and were treated with 400 mg metronidazole thrice daily for 7 days with 0.2 percent chlorhexidine as mouthwash twice daily for 1 month. All patients had the calculus cleared before start of the trial. Patients were treated for 4 weeks, assessed every 7 days, and followed up for a further 1 month. The efficacy of the drug *triphala* was considered comparable to the modern drug, which however had faster onset of action, but also the modern drug had more rapid recurrence of symptoms.⁸ Further studies are indicated.

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OPHTHALMOLOGICAL AGENTS

Plants have been used in Ayurveda to treat different eye conditions, including refractive disorders, cataract in the initial stages, and glaucoma. Although eye conditions have not been accorded a separate branch in Ayurveda, such as surgery, a large number of plants have been used.¹ In a survey¹ of seven major texts of Ayurveda, 41 single drugs are found to have been mentioned for 29 eye conditions. The various factors, which are considered to contribute to the development of eye diseases, have also been discussed.¹ Plant combinations have been mainly used for conditions such as cataract and refractive errors. The traditional formulation known as *Mahatriphaladi Ghrita* (MTG), a preparation made of various herbs cooked in *ghee* or clarified butter, which is in itself considered good for the eyes, is popularly used by Ayurvedic physicians to improve eyesight when taken internally and also applied to the eyes.² In a trial on 150 patients with primary open-angle glaucoma, patients were divided into three groups, group 1 served as control and patients were treated locally with standard

antiglaucoma drug four times a day, group 2 received two tablespoons of MTG twice a day with warm milk, whereas group 3 received 2 percent pilocarpine with MTG, all medications for 90 days. Group 3 receiving MTG together with pilocarpine showed optimum improvement, with pilocarpine contributing to quick relief and MTG to prolonged maintenance of intraocular pressure. No side effects were seen in the MTG group, although in the pilocarpine group side effects (not specified) were reported, which were reduced in the combination group.³ The effect of MTG on lipid parameters needs to be investigated in view of the use of clarified butter or *ghee* as base.

Conjunctivitis

Conjunctivitis is a common infectious condition of the eyes associated with redness, sticky discharge, burning and irritation, grittiness, swelling, and visual disturbances caused by pathogens of bacterial, fungal, or viral origin, and due to allergens. A review of different plant species that have been used to treat conjunctivitis has been published.⁴ The modest amount of scientific work has been mostly in this area; exploratory trials with some plants having been carried out. *Curcuma longa*, with its anti-inflammatory, antioxidant, and antibacterial property, has been used to treat not only conjunctivitis, but also curcumin, the active principle has been used and tried out in chronic anterior uveitis and in orbital pseudo tumors. Other plants for which preliminary exploratory trials have been carried out are *Berberis aristata*, *Cyperus rotundus*, and *Glycyrrhiza glabra* for conjunctivitis and *Rubia cordifolia* for painful eye conditions.

Albizzia lebbbeck Benth. (Family: Mimosaceae)

Sanskrit: Sirisha

Tamil: Vagei

Hindi: Siris

English: East Indian Walnut
Tree, Siris Tree

In a comparative study on allergic conjunctivitis, 60 patients were enrolled for the study and divided into three groups of 20

each. The trial preparation was made from the aqueous extract of the bark concentrated to dryness (*ghanasatwa*). Each capsule had 500 mg of the extract and the drops were made from 2 g percent of the extract. Group 1 that served as control received standard dexamethasone two drops thrice daily for 60 days. Group 2 received *Albizzia lebbeck* eye drops two drops thrice daily for 60 days, whereas the third group received, in addition to the *Albizzia lebbeck* eye drops, one capsule containing 500 mg of *Albizzia lebbeck* extract thrice daily again for 60 days. There was a relapse rate of 100 and 60 percent in the first two groups and the third group had only a 25 percent rate of recurrence.⁵

***Berberis aristata* DC (Family: *Berberidaceae*)**

Sanskrit: Daruharidra	Tamil: Maramanjai
Hindi: Darhald	English: Barberry

In an open trial, eyedrops made from semisolid extracts of *Berberis aristata*, honey, and distilled water were tried on 100 patients with conjunctivitis including cases not responding to antibiotics. Two to four drops of “*Madhudarvyadi*” eyedrops were instilled in each eye thrice a day. A total of 98 patients with different kinds of conjunctivitis obtained relief. About 59 percent of patients obtained relief in 1-2 days, a further 29 percent in 2-4 days, and the remaining 10 percent in 4-10 days.⁶

***Curcuma longa* Linn. (Family: *Zingiberaceae*)**

In a comparative trial, 50 patients with conjunctivitis were treated: 25 patients with turmeric eyedrops and 25 patients with 5 percent soframycin eyedrops. The eyedrops were instilled four to five times a day for 7 days. In patients on turmeric eyedrops, symptoms improved day 3 with complete improvement by day 6, except for two cases. Patients on soframycin also improved from day 4 and complete relief took 7 days except for two patients, who needed 9 days for complete relief.⁷ Thus, treatment with turmeric eyedrops was comparable to

soframycin; however, further trials are required with larger patient numbers. No side effects were observed.⁷

***Cyperus rotundus* Linn. (Family: Cyperaceae)**

Sanskrit: Mustaka, Musta	Tamil: Korai
Hindi: Mutha, Moth	English: Nut grass

In an open study, the effect of an aqueous solution of a methanolic extract of *Cyperus rotundus* tubers was studied in patients with conjunctivitis. Most of the patients were relieved of pain and redness and considered cured after 5 days.⁸

***Glycyrrhiza glabra* Linn. (Family: Fabaceae)**

Sanskrit: Yashtimadhu	Tamil: Atimadhuram
Hindi: Mulethi	English: Liquorice, Licorice

In a comparative study, 50 patients with acute conjunctivitis were divided into two groups of 25 patients each. The first group was treated with a 5 percent aqueous solution of *Glycyrrhiza glabra* eye drops, whereas the second group was treated with chloramphenicol eyedrops, both medications being instilled six times a day by the patients while observing hygiene. Patients receiving *Glycyrrhiza glabra* eyedrops showed decrease in symptoms from day 4 onwards with complete disappearance of the symptoms in 5-7 days. There were four patients who did not respond to the treatment. In the chloramphenicol group, all 25 patients responded in 4-7 days. Symptoms such as itching, congestion, and swelling of lids subsided faster in the *Glycyrrhiza glabra* group compared to the chloramphenicol group, probably because of glycyrrhizin present, that has corticosteroid-like action.⁹

Chronic Anterior Uveitis***Curcumin***

A study was carried out involving 53 patients of chronic anterior uveitis, which is characterized by pain and redness in the eye, sensitivity to light, watering of eyes, and diminution of vision, with black spots in some patients. Thirty-two patients, who were available for the trial, were divided into two groups. All 32 patients were treated orally with 375 mg of 95 percent curcumin thrice daily for 12 weeks, in addition to topical mydriatics and local hot fomentation, although one group of 14 patients, who tested positive for PPD-induced delayed sensitivity, received antitubercular drugs for 1 year, since it has been postulated that uveitis arises due to tuberculosis. The remaining 18 patients received curcumin alone. A marked clinical improvement was observed in both groups with improvement in vision, decrease in aqueous flare, and keratic precipitates, and break of anterior and posterior synechiae. Improvement was slow initially but became satisfactory after 2 weeks. No side effects due to curcumin were observed.¹⁰ The results warrant further clinical studies.

Idiopathic Inflammatory Orbital Pseudotumors***Curcumin***

In a small exploratory trial on eight patients with idiopathic inflammatory orbital pseudotumors, 375 mg curcumin was administered orally thrice daily for 6-22 months. Patients were followed up every 3 months for a total of 2 years. Of the five patients who completed the study, four patients recovered completely, whereas in the remaining one patient, swelling came down completely; however, there was restriction in movement. No side effects were observed.¹¹ Further studies are warranted.

Painful Ophthalmic Conditions

***Rubia cordifolia* Linn. sensu Hook f. (Family: Rubiaceae)**

Sanskrit: Manjistha	Tamil: <i>Manjitti</i>
Hindi: Manji, Majit	English: The Indian Madder

Various preparations such as decoction, powder, and *ghrita* (preparation with clarified butter or *ghee* as base) of *Rubia cordifolia* were tried in painful ophthalmic conditions both internally and topically and found to relieve pain without any side effects. Further details are not available in the abstract and this study is mentioned for record.¹²

Glaucoma

Glaucoma is characterized by increasing intraocular pressure causing compression of the blood vessels to the retina resulting, over time, in loss of vision.

***Coleus forskohlii* Briq. (Family: Lamiaceae)**

Forskolin, the active principle from *Coleus forskohlii*, has been evaluated for use in glaucoma only in healthy volunteers, which has been reviewed.¹³

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Appendix

List of Single Plants, Indications, and Chapters

Chapter numbers in bold print have introductory remarks about the plant.

Plant Name	Indication (Chapter Number)
1 <i>Adhatoda vasica</i>	Antiulcer agent (3), Bronchial asthma (5), Pyorrhea (14)
2 <i>Aegle marmelos</i>	Diarrhea (3)
3 <i>Albizzia lebbeck</i>	Bronchial asthma (5), TPE (5), Conjunctivitis (14)
4 <i>Aloe barbadensis</i>	Psoriasis (9), Wound healing (9)
5 <i>Anacyclus pyrethrum</i>	Local anesthetic (14)
6 <i>Andrographis paniculata</i>	Hepatoprotective agent (4), Common cold and flu (5)
7 <i>Asparagus racemosus</i>	Antiulcer agent (3), Galactagogue (10), Diabetic retinopathy (11)
8 <i>Azadirachta indica</i>	Skin diseases (9), Wound healing (9), Antidiabetic agent (11), Dental health (14)
9 <i>Bacopa monnieri</i>	Memory enhancement (12)
10 <i>Berberis aristata</i>	Viral hepatitis (4), Conjunctivitis (14)
11 <i>Berberis vulgaris</i> (berberine)	Chronic cholecystitis (4)
12 <i>Boerhaavia diffusa</i>	Ascites (4), Diuretic (7)
13 <i>Boerhaavia repanda</i>	Leukorrhea (10)
14 <i>Boswellia serrata</i>	Inflammatory bowel disease (3), Bronchial asthma (5), Rheumatoid arthritis (8), Cancer therapy (13)
15 <i>Cardiospermum halicacabum</i>	Skin diseases (9)
16 <i>Cassia angustifolia</i>	Laxative (3)
17 <i>Celastrus paniculatus</i>	Memory and learning enhancement (12)

Plant Name	Indication (Chapter Number)
18 <i>Centella asiatica</i>	Venous disorders (6), Psoriasis (9), Wound Healing (9), Memory and learning enhancement (12), Tonic antiaging effects (13), Immunostimulant effect (13)
19 <i>Cinnamomum tamala</i>	Antidiabetic agent (11)
20 <i>Cissus quadrangularis</i>	Fracture healing (9)
21 <i>Clerodendron phlomidis</i>	Antidiabetic agent (11)
22 <i>Coccinia grandis</i>	Antidiabetic agent (11)
23 <i>Coleus forskohlii, forskolin</i>	Hypertension (6), Glaucoma (14)
24 <i>Commiphora wightii</i>	Hypolipidemic agent (6), Rheumatoid arthritis (8)
25 <i>Convolvulus pluricaulis</i>	Memory and learning enhancement (12)
26 <i>Crataeva nurvala</i>	Urinary stones (7), Urinary infection (7), Benign prostatic enlargement (7)
27 <i>Curcuma longa, curcumin</i>	Dyspepsia (3), Bronchial asthma (5), Rheumatoid arthritis (8), Cancer therapy (13), Conjunctivitis (14), Chronic anterior uveitis (14), Idiopathic orbital pseudotumors (14)
28 <i>Cyperus rotundus</i>	Diarrhea (3), Conjunctivitis (14)
29 <i>Eclipta alba</i>	Antiulcer plant (3), Hepatoprotective agents (4)
30 <i>Embolica officinalis</i>	Antiulcer plant (3), Hypolipidemic agent (6), Tonic antiaging agent (13)
31 <i>Glycyrrhiza glabra</i>	Antiulcer (3), Conjunctivitis (14)
32 <i>Gymnema sylvestre</i>	Antidiabetic agent (11)
33 <i>Holarrhena antidysentrica</i>	Diarrhea (3)
34 <i>Inula racemosa</i>	Cardioprotective plant (6)
35 <i>Mimosa pudica</i>	Menorrhagia (10)
36 <i>Momordica charantia</i>	Antidiabetic agent (11)
37 <i>Mucuna pruriens</i>	Parkinson's disease (12)
38 <i>Musa sapientum</i>	Antiulcer plant (3)
39 <i>Nardostachys jatamansi</i>	Sedative plant (12)
40 <i>Ocimum sanctum</i>	Bronchial asthma (5), TPE (5), Viral encephalitis (5)
41 <i>Phyllanthus amarus</i>	Viral hepatitis (4), Antidiabetic agent (11)
42 <i>Picrorhiza kurroa</i>	Laxatives (3), Hepatoprotective agent (4)
43 <i>Piper longum</i>	Bronchial asthma (5)
44 <i>Plantago ovata</i>	Laxatives (3)
45 <i>Pongamia pinnata</i>	Skin diseases (9)
46 <i>Psoralea corylifolia</i>	Leukoderma (9)
47 <i>Pterocarpus marsupium</i>	Antidiabetic agent (11)
48 <i>Ricinus communis</i>	Laxative (3)
49 <i>Rubia cordifolia</i>	Diabetic foot (11), Painful ophthalmic conditions (14)
50 <i>Salacia spp.</i>	Antidiabetic agent (11)

Plant Name	Indication (Chapter Number)
51 <i>Saraca asoca</i>	Metromenorrhagia (10)
52 <i>Semecarpus anacardium</i>	Rheumatoid arthritis (8)
53 <i>Sida cordifolia</i>	Diabetic neuropathy (11)
54 <i>Solanum trilobatum</i>	Bronchial asthma (5)
55 <i>Solanum xanthocarpum</i>	Bronchial asthma (5)
56 <i>Syzygium cuminii</i>	Antidiabetic agent (11)
57 <i>Terminalia arjuna</i>	Cardioprotective plant (6)
58 <i>Terminalia belerica</i>	Bronchial asthma (5), Diarrhea (3)
59 <i>Terminalia chebula</i>	Laxative (3)
60 <i>Tinospora cordifolia</i>	Hepatoprotective agent (4), Rheumatoid arthritis (8), Immunostimulant effects (13), Cancer therapy (13)
61 <i>Tribulus terrestris</i>	Diuretic (7)
62 <i>Trigonella foenum graecum</i>	Hypolipidemic agent (6), Antidiabetic agent (11)
63 <i>Tylophora indica</i>	Bronchial asthma (5), Allergic rhinitis (5)
64 <i>Valeriana wallichii</i>	Sedative plant (12)
65 <i>Vitex negundo</i>	Antirheumatic agent (8)
66 <i>Withania somnifera</i>	Rheumatoid arthritis (8), Memory enhancement (12), Tonic antiaging agent (13), Cancer therapy (13)
67 <i>Wrightia tinctoria</i>	Psoriasis (9), Nonspecific dermatitis (9)
68 <i>Zingiber officinale</i>	Malabsorption syndrome (3) Antiemetic agent (3), Rheumatoid arthritis (8)

Index

- Abdominal sepsis, 21
- Abortifacient effect, vasicine, 87
- Abutilon indicum*, 111, 115
- Acacia, in dental care, 330
- Acemannan, 212, 213
- Acetyl- β -boswellic acid, 34, 318
- Acetyl-11-keto- β -boswellic acid, 34, 318
- Acid dyspepsia, *Asparagus racemosus*, 22
- Aconitum*, 4
- Acoustic startle response, 285
- Acute phase reactants, 180
- Acute viral hepatitis, 78
- Adaptogenic activity, 305, 308
- Adhatoda vasica*, 85
 - clinical trial, 29, 87, 332-333
 - collection, season for, 3
 - constituents, 87
 - description, 86
 - other names, 86, 332
 - pharmacology, 87
 - safety, 87-88
 - traditional use, 86-87
- Adhatoda zeylanica*. *See* *Adhatoda vasica*
- Adhatodai*. *See* *Adhatoda vasica*
- Adrak*. *See* *Zingiber officinale*
- Adraka*. *See* *Zingiber officinale*
- Aegle marmelos*, 54-55
- Aging and free radical damage, 306, 307
- Alantolactone, 126
- Albizzia lebbbeck*, 88-90, 336-337
 - allergic conjunctivitis, 336-337
 - bronchial asthma, 89-90
 - constituents, 88
 - description, 88
 - flowers in TPE, 90, 116
 - other names, 88, 336
 - pharmacology, 88-89
 - safety, 90
 - use, 88
- Albizziasaponins*, 88
- Aldose reductase activity, 250, 251
- Alkaloids,
 - in *Aconitum*, 4
 - in *Adhatoda vasica*, 3, 87
 - in *Aegle marmelos*, 54
 - in *Bacopa monnieri*, 281
 - in *Berberis vulgaris*, 82
 - in *Boerhaavia diffusa*, 152
 - in *Celastrus paniculatus*, 286
 - in *Coccinia indica*, 234
 - in *Convolvulus pluricaulis*, 288
 - in *Crataeva nurvala*, 157
 - in *Embllica officinalis*, 22
 - in *Holarrhena antidysentrica*, 56
 - in *Mucuna pruriens*, 299
 - in *Phyllanthus amarus*, 77
 - in *Piper longum*, 4, 95
 - in *Piper nigrum*, 4
 - in *Solanum xanthocarpum*, 9, 98, 100
 - in *Tinospora cordifolia*, 69
 - in *Tribulus terrestris*, 154, 155
 - in *Trigonella foenum graecum*, 256
 - in *Tylophora indica*, 101, 102
 - in *Vitex negundo*, 176
 - in *Withania somnifera*, 179
- Allergic reaction, *Plantago ovata*, 47
- Allergic rhinitis, *Tylophora indica*, 102, 104
- Aloe barbadensis*, 211-214
 - constituents, 212
 - description, 211-212
 - other names, 211
 - pharmacology, 212-213
 - psoriasis, 208
 - safety, 214
 - use, 212
 - wound healing, 213-214
- Aloe* gel, factors in use, 213-214
- Aloeride, 212, 213

- Aloe vera*, 207, 208, 212-214. *See also*
Aloe barbadensis
 Alpha-glucosidase inhibitor, 250, 251
 Alzheimer's disease
 and *Bacopa monnieri*, 281
 and bioactive withanolides, 290
 and *Celastrus paniculatus*, 287
 and *Centella asiatica*, 285
 Amalaki rasayan, 24, 307, 308
 Amalaki. *See Emblica officinalis*
 Amantidine, 113, 114
 Amavata. *See* rheumatoid arthritis
 Amavatari rasa, 183
 Amenorrhea, 212
 American Rheumatic Association, 164,
 173, 178, 183
 Amla. *See Emblica officinalis*
 Ammaikodi. *See Asparagus racemosus*
 Ammanaku. *See Ricinus communis*
 and castor
 Ammukara. *See Withania somnifera*
 Amoebiasis, 54
 and *Aegle marmelos*, 55
 and ginger, 15
 and *Holarrhena antidysenterica*, 57, 58
 and *Terminalia belerica*, 58
 Ampicillin, 55, 171
 Amrita. *See Tinospora cordifolia*
 Amrit bhallataka and *Boswellia*
 serrata, 173-174
 δ -Amyrin, 219
 δ -Amyrone, 219
 Anacardic acid, 172
Anacyclus pyrethrum, 333-334
 Anakoranti. *See Salacia macrocarpa*
 Analgesic activity, 170, 279
 and *Anacyclus pyrethrum*, 333
 and *Azadirachta indica*, 195
 and bavichinin, 205
 and *Boswellia serrata*, 34, 317
 and *Commiphora mukul*, 167
 and *Pongamia pinnata*, 199, 200
 and *Semecarpus anacardium*, 172
 and *Terminalia belerica*, 100
 and *Tinospora cordifolia*, 69, 175
 and *triphal*a, 332
 and *Vitex negundo*, 176, 177
 and *Wrightia tinctoria*, 209
Andrographis paniculata, 3i, 62, 63-64,
 111
 clinical trials, 64, 112-114
 constituents, 63
 description, 63, 111
 other names, 63, 111
 pharmacology, 63-64, 112
 safety, 64, 114
 traditional use, 63, 111
 Andrographolide, 63, 64, 112, 113
 Angina, 119, 120, 122-123, 124, 137
 Angiogenesis, 215
 Ankylosing spondylitis, 164, 168, 178
 Antamul. *See Tylophora indica*
 Anthrapachaka. *See Tylophora indica*
 Anthraquinone glycosides in *Albizzia*
 lebeck, 88
 Antiallergic activity, 85
 and *Adhatoda vasica*, 87
 and *Albizzia lebeck*, 88, 89
 and andrographolide, 112
 and *Curcuma longa*, 18, 91
 and *Piper longum*, 95
 and *Solanum xanthocarpum*,
 97-98
 and *Tylophora indica*, 102
 Anti-ADH, 224
 Antianxiety effect, 281, 284
 Antiarthritic activity
 Boswellia serrata, 34
 Commiphora mukul, 166, 167
 *triphal*a, 104
 Vitex negundo, 176, 177
 withaferin A, 179
 Antibacterial activity, 330-331
 and *Aloe vera*, 212
 and *Azadirachta indica*, 195, 328
 and *Crataeva nurvala*, 160
 and *Curcuma longa*, 336
 and *Cyperus rotundus*, 56
 and *Pongamia pinnata*, 200
 and *Psoralea corylifolia*, 206
 and *Terminalia belerica* 58
 and *triphal*a, 334
 Anticancer activity, 8, 169, 247, 317,
 318, 320
 Anticholestatic activity, 68, 82
 Anticoagulant therapy and ginger, 15
 Antidepressant, 281, 290

- Antidiabetic agents, 229-230, 231-277
 Antiemetic agents, 14, 39-41
 Antifibrotic effect, 70
 Antifungal, *neem*, 195
 Antihyperlipidemic plants, 119
 Antihypertensives, 119, 144, 145, 154-155
 Anti-inflammatory activity, 9, 10, 65
 agents with, 163, 165
 and *Aloe*, 212
 and andrographolide, 112
 and bavichinin, 205
 and *Boerhaavia diffusa*, 81, 152
 and *Boswellia serrata*, 34, 164
 and *Cardiospermum halicacabum*, 198
 and *Commiphora mukul*, 132, 166, 167
 and *Crataeva nurvala*, 158, 159
 and *Curcuma longa*, 17, 91, 169, 170
 and *Eclipta alba*, 66
 and ginger, 14, 182
 and *Glycyrrhiza glabra*, 31
 and *neem*, 195
 and *Pongamia pinnata*, 199, 200
 and *Semecarpus anacardium*, 172
 and *Tinospora cordifolia*, 70, 175
 and *Tylophora indica*, 102
 and *Vitex negundo*, 177
 and *Withania somnifera*, 179, 180
 and *Wrightia tinctoria*, 209
 Antimicrobial, 330
 Antimutagenic activity, 15, 25, 39
 Antioxidant activity, 305, 306
 and guggulsterone, 133
 and *Aloe*, 212-213
 and apigenin, 93
 and arabinogalactan, 313
 and *Bacopa monnieri*, 281
 and bakuchiol, 205
 and bioactive withanolides, 290
 and *Celastrus paniculatus*, 287
 and *Centella asiatica*, 215, 285
 and *Convolvulus pluricaulis*, 289
 and *Curcuma longa*, 10, 169
 and *Eclipta alba*, 65
 and *Embllica officinalis*, 22
 and isobavachalcone, 205
 and isobavachin, 205
 and lupeol, 159
 Antioxidant activity (*continued*)
 and *Mucuna pruriens*, 299
 and *Nardostachys jatamansi*, 302
 and *Picrorhiza kurroa*, 67
 and rosmarinic acid, 93
 and *Semecarpus anacardium*, 172
 and *Syzygium cumini*, 254
 and *Terminalia arjuna*, 122
 and *Vitex negundo*, 176
 and *Withania somnifera*, 308
 Antioxytotic, 224
 Antipyretic activity, 112, 175, 205, 279
 Antirheumatic activity, 167, 170-171
 Antirheumatic agents,
 Boswellia serrata, 164-166
 Commiphora wightii, 166-169
 Curcuma longa, 169-171
 Ricinus communis, 47
 Semecarpus anacardium, 171-175
 Tinospora cordifolia, 175-176
 Vitex negundo, 176-178
 Withania somnifera, 179-181
 Zingiber officinale, 181-184
 Antisecretory activity
 of *Glycyrrhiza glabra*, 31
 of *Embllica officinalis*, 23
 Antistress activity, 179, 281
 Antitussive activity, 87, 95, 98, 100, 101
 Anti-ulcer activity
 and *Adhatoda vasica*, 29
 and *Asparagus racemosus*, 21-22
 and *Eclipta alba*, 30
 and *Embllica officinalis*, 23-24
 and *Glycyrrhiza glabra*, 31
 and *Musa sapientum*, 25, 26
 Antiulolithiatic agent, 154, 157, 159
 Antiviral activity, 83
 amantidine, 114
 neem, 195
 Phyllanthus amarus, 77
 picroliv, 80
 Pongamia pinnata, 200
 turmeric, 169
 Anxiety, 280
 and *Bacopa monnieri*, 281-283
 and *Centella asiatica*, 284, 285
 and *Centella asiatica* and
 Hypericum perforatum, 52

- Anxiety (*continued*)
 and *Convolvulus pluricaulis*, 288-289
 and *Nardostachys jatamansi*, 302
 and *Withania somnifera*, 290-291
- Apigenin, 93, 198
- Apoptosis, 323. *See also* cell death
- Arabinogalactan, 313
- Arista, 290. *See* *ashwagandha arista*; *kutajarista*
- Arjuna. *See* *Terminalia arjuna*
- Arjunolic acid, 121-122
- Arkarni. *See* *Tylophora indica*
- Arni. *See* *Clerodendron phlomidis*
- Arogyavardini vati, 196
- Arusa. *See* *Adhatoda vasica*
- Ascaris lumbricoides*, 55
- Ascites, 81-82, 152, 317-318
- Asgandh. *See* *Withania somnifera*
- Ashwagandha arista, 290
- Ashwagandha. *See* *Withania somnifera*
- Ashwagola. *See* *Plantago ovata*
- Asiatic acid, 147, 214
- Asiaticoside, 147, 214, 215
- Asmari. *See* urinary stones
- Asparagus racemosus*, 305
 constituents, 20-21
 description, 20
 diabetic retinopathy, 276-277
 galactagogue, 223-224
 other names, 20
 pharmacology, 21
 safety, 22
 traditional use, 20
 ulcer and other conditions, 21-22
- Asparagus. *See* *Asparagus racemosus*
- Astanga hrdayam*, 2, 120, 121
- Asthma. *See* bronchial asthma
- Astrocytoma and glioblastoma, 318-319
- Atharva veda, 2, 132
- Atimadhuram. *See* *Glycyrrhiza glabra*
- Atopic dermatitis, 198
- Atri, 2
- Aucubin, 45, 176
- Axon extension, 290
- Ayurveda, 1-2, 7, 43. *See also* individual herbs and disease conditions
 alcoholic extracts in, arista, 290
 bioavailability, 4-5
 controversial drugs in, 184, 289
 disease and digestion, 13, 14, 85, 163-164, 181
 disease entities in, 8
 drug classification, 279
 drug selection in, 2
 health in, 1
 health of colon in, 43
 history of research, 7-8
 meaning of, 2
 origins of, 1-2
 plant use in, 3, 4-5, 61
 role of psyche in disease, 279
 synergy, 5
 'vehicle' in, 92
- Azadirachta indica*, 17, 69, 208
 clinical trials, 195-196, 218, 233, 330-331
 constituents, 231
 description, 231
 other names, 194, 231
 pharmacology, 195, 232-233, 328
 safety, 196, 233-234
 use, 194-195, 231, 330
- Azadirachta indica*. *See also* neem
- Azadirachta indica*, 196
- Bacopa monniera*. *See* *Bacopa monnieri*
- Bacopa monnieri* 5, 46, 280-283
Centella asiatica and, 280
 clinical trials, 281-283
 combination, 55, 127
 constituents, 280-281
 description, 280
 other names, 280
 pharmacology, 281
 safety, 282, 283
 use, 280
- Bacopasaponin C, 281
- Bacoside A, 280-281
- Bacoside B, 281
- Bacoside A₃, 281
- Bael. *See* *Aegle marmelos*
- Bahera. *See* *Terminalia belerica*

- Banana. *See Musa sapientum*
- Banaras Hindu University, 7, 29, 30, 111
- Barbados Aloe. *See Aloe barbadensis; A. vera*
- Barberry. *See Berberis aristata*
- Bauhinia variegata*, 276
- Benign prostatic enlargement, 159 and *Crataeva nurvala*, 158-159
- Bel. *See Aegle marmelos*
- Beleric myrobalan. *See Terminalia belerica*
- Bengal quince. *See Aegle marmelos*
- Benign Prostatic Hypertrophy, 158
- Berberine, 69, 82
- Berberis aristata*, 62, 80, 336, 337
- Beta cell regeneration, 239, 242, 243, 246
- Betulinic acid, 158, 176
- Bhallatak. *See Semecarpus anacardium*
- Bhallataka. *See Semecarpus anacardium*
- Bhangra. *See Eclipta alba*
- Bharadwaja, 2
- Bhavaprakash*, 303
- Bhilawa. *See Semecarpus anacardium*
- Bhilwanol, 172
- Bhringaraj. *See Eclipta alba*
- Bhuiavala. *See Phyllanthus amarus*
- Bhumyamalaki. *See Phyllanthus amarus*
- Bhunimba. *See Andrographis paniculata*
- Bibhitaka. *See Terminalia belerica*
- Biflavonoids, 172
- Bile Acid Receptor Antagonist, 133
- Bilva. *See Aegle marmelos*
- Bioactive withanolides, 290. *See also* withanolides
- Bioavailability, 4, 5, 170
- Bisdemethoxycurcumin. *See* curcumin II
- Biskhafra. *See Boerhaavia diffusa*
- Bitter melon. *See Momordica charantia*
- Bittergourd. *See Momordica charantia*
- Blackberry. *See Syzygium cuminii*
- Black oil plant. *See Celastrus paniculatus*
- Black plum. *See Syzygium cuminii*
- Blood pressure and *Holarrhena antidysentrica*, 57 and *Bacopa monnieri*, 282 and *Coleus forskohlii*, 145 and combination preparation, 128 and *Convolvulus pluricaulis*, 289 and *Glycyrrhiza glabra*, 31 and *Phyllanthus amarus*, 275 and *Terminalia arjuna*, 121, 122, 123, 125 and *Tribulus terrestris*, 154-155 and *Withania somnifera*, 291
- Boerhaavia diffusa*, 62, 81-82, 151-154, 223 clinical trials, 81, 152-153, 309-310, 312 constituents, 152 description, 152 other names, 151 pharmacology, 81, 152 safety, 153-154 traditional use, 152
- Boerhaavia repanda* in leukorrhea, 225
- Boerhaavia repens*. *See Boerhaavia diffusa*
- Bonesetters, 193, 219
- Bones, degenerative changes, 180
- Boswellia serrata*, 2i, 9, 10, 33, 34-39, 163 clinical trials, 35-37, 91, 164-166, 173-174, 318-319 constituents, 34 description, 34 other names, 34 pharmacology, 34-35, 36, 90, 164, 317-318 safety, 319 side effects and safety, 37, 91, 319 traditional use, 34, 90
- Boswellic acids, 10, 34, 35, 90, 164, 319 β -Boswellic acid, 34, 318
- Bradycardia, 121
- Brahma-manduki. *See Centella asiatica*
- Brahmi identity, 280
- Brahmi. *See Bacopa monnieri*
- Brahminoside, 147, 284
- Brahmoside, 147, 284
- Brain tonic, 280, 284

- Brihatrayi, 2
 Bronchial asthma, clinical studies
 and *Adhatoda vasica*, 87
 and *Albizzia lebbbeck*, 89-90
 and *Boswellia serrata*, 91
 and *Curcuma longa*, 91-92
 and *Ocimum sanctum*, 93-94
 and *Piper longum*, 95-96
 and *Solanum trilobatum*, 99
 and *Solanum xanthocarpum*, 98-99
 and *Tylophora indica*, 102-104
 Bronchial asthma, symptoms, 85
 Bronchiectasis, *Curcuma longa*, 92
 Bronchitis, 95, 97, 98, 111
 and *Adhatoda vasica*, 86
 and *Boswellia serrata*, 90
 and *Curcuma longa*, 91-92
 and *Ocimum sanctum*, 93
 Bronchodilatory activity, 101, 102
 Bufexamac, 198
- Caffeic acid, 93, 253
 Cakradatta, 121
 Cakrapanidatta, 121
 Calcium oxalate, 220, 221, 227
Camellia sinensis, 330
 Cancer
 oral, 326
 breast, 323
 colorectal, 321
 and constipation, 44
 herbs for, 317-323, 326
 in Ayurveda, 317
 Boswellia serrata, 317-319
 Curcuma longa, 319-321
 Curcumin, 321
 Tinospora cordifolia, 322-323
 Withania somnifera, 326
Candida albicans, 195
Caraka samhita 2, 132
 on *Adhatoda vasica*, 86
 on *Andrographis paniculata*, 63
 on collection season, 3
 on *Commiphora wightii*, 132
 on diabetes as madhumeha/
 prameha, 229
 on heart disease, 120
 on *Inula racemosa* for chest pain, 126
 on jaundice, 61, 77
- Caraka samhita* (continued)
 on meetings, 2
 on *Piper longum*, 95
 on rasayana, 305
 Caraka, 2
 on *amavata*, 164
 on *Convolvulus pluricaulis*, 288,
 289
 on heart disease, 119, 120
 on *Inula racemosa*, 126
 on *Nardostachys jatamansi*, 302
 on plants for respiratory disorders, 86
 on *rasayana*, 306
 on *Ricinus communis*, 47
 on *Solanum xanthocarpum*, 97
 on *Terminalia arjuna*, 120
 on turmeric, 169
 on *Valeriana wallichii*, 303
 Cardenolide, 88
 Cardioprotective plants, 119, 120
 Terminalia arjuna, 120-125
 Inula racemosa, 125-128
Cardiospermum halicacabum, 197-199
Cardiospermum halicacabum var.
 luridum, 197
Cardiospermum halicacabum var.
 microcarpum, 197
 Cardiotonic, 121, 152
 Cardiovascular disorders, 119
 Carminative,
 bitter gourd as, 241
 black plum as, 253
 fenugreek as, 256
 ginger as, 14, 182
 long pepper as, 85
 turmeric as, 17
 Carnosine, 220, 221
Cassia angustifolia, 43-45
Cassia fistula, 45
 Castor, 43. *See also Ricinus communis*
 Cataract, 230, 242, 247, 254, 330
Catharanthus roseus, 232
Celastrus paniculatus, 286-288
 Cell death, 318, 322
 Cellular immune response, 70,
 102, 195
 Cellular toxicity, 25, 57, 58

- Centella asiatica*, 8i, 111, 127,
146-148, 207, 283-286, 288
and *Bacopa monnieri*, 280
constituents, 147
description, 146, 316
memory and learning, 285
other names, 146
pharmacology, 214-215, 284-285, 316
psoriasis, 208
safety, 148, 285-286
tonic/antiaging effect, 312
traditional use, 146-147, 214,
283-284, 316
URTI, 316
venous disorders, 147-148
wound healing, 215
- Central Council for Research in
Ayurveda and Siddha, 7
- Central nervous system agents. *See*
CNS agents
- Cephalandra indica*. *See* *Coccinia*
grandis
- Cervical spondylosis, 168, 178, 181
- Charantin, 241, 244
- Chebularic acid, 49, 58
- Chebolic myrobalan. *See* *Terminalia*
chebula
- Chemotypes, 289
- Cherukoranti. *See* *Salacia prinoidea*
- Chewing sticks, 231, 329, 330, 331
- Children
and bronchial asthma, 96, 97
and common cold, 112-113
and constipation, 44
and dental health, 330-331
and intracranial tumors, 319
and general health, 308, 309-310
and infective hepatitis, 78
and jaundice, 66
and memory, 283, 284
and mental retardation, 285, 287
and nausea, 40
and stomach complaints, 56
and TPE, 116-117
and URTI, recurrent, 115-116
- Chlordiazepoxide, 55
- Chlorhexidine, 331, 334
- Chlorpropamide, 236, 248, 254, 255
- Choleretic activity, 82
and andrographolide, 64
and *Picrorhiza kurroa*, 53, 68
and turmeric, 17, 18, 169
- Cholestasis, 18, 68, 70
- Chopra, R.N., 7
- Chronic anterior uveitis, 336, 339
- Chronic cholecystitis, 82
- Chronic colitis, 35, 36
- Chronic hepatitis B, 76, 77-78
- Chronic polyarthritis, 167
- Chyavan, 10
- Chyavanprash, 10
- Cinnamomum tamala*, 273-274
- Ciprofloxacin, 5
- Cisplatin, 41
- Cissus quadrangularis*, 10i, 219-221
- Clerodendron phlomidis*, 274
- Clerodendrum multiflorum*. *See*
Clerodendron phlomidis
- Clerodendrum phlomidis*. *See*
Clerodendron phlomidis
- Clidinium bromide, 55
- Climbing staff tree. *See* *Celastrus*
paniculatus
- CNS agents, 279, 280-303
- CNS drugs in Ayurveda, 279
- Coccinia grandis*, 234-236
clinical trials, 235-236
constituents, 234
other names, 234
pharmacology, 234-235
safety, 236
use, 234
varieties, 235
- Coccinia indica* var. *palmata*, 234, 235
- Coccinia indica* Wight & Arn, 235
- Coccinia indica*. *See* *Coccinia*
grandis
- Cognitive enhancing properties, 285,
286, 287, 288, 289, 290
- Cognitive function, 282, 283
- Coleonol, 145
- Coleus barbatus*. *See* *Coleus*
forskohlii
- Coleus forskohlii*, 144-145, 340
clinical trials, 145
forskolin in glaucoma, 340
constituents, 145

- Coleus forskohlii* (continued)
 description, 144
 other names, 144
 safety, 145
 traditional use, 145
- Colic, 14, 63, 77
- Collagen synthesis, 214, 215
- Commiphora mukul*, 4, 5, 9, 126, 127, 128, 163. *See also* *C. wightii*
- Commiphora mukul*, *Dalbergia lanceolaria* and *Semecarpus anacardium*, 5, 168, 174
- Commiphora mukul* and *Vitex negundo*, 177-178
- Commiphora mukul* and *Zingiber officinale*, 182, 183, 184
- Commiphora wightii*, 7i, 131-138, 166-169
 clinical trials, 133-137, 167-169, 177
 constituents, 132
 description, 132
 history of use, 132
 other names, 131, 166
 pharmacology, 132-133, 166-167
 processing, gum resin of, 4
 side effects and safety, 137-138
- Common cold, 87, 111-113
- Complement system, 316
- Conessi. *See* *Holarrhena antidysentrica*
- Congestive heart failure, 123-124
- Conjunctivitis, 336
 plants for, 336-338
- Controversial drugs. *See under* Ayurveda
- Convolvulus prostratus*. *See* *Convolvulus pluricaulis*
- Cordifolioside A, 69, 313
- Cordifolioside B, 69
- Cordioid, 69, 313
- Cordioside, 69, 313
- Corilagin, 22, 49, 253
- Coronary artery disease, 120, 124
- Country ipecacuanha. *See* *Tylophora indica*
- Covolvulus microphyllus*. *See* *Convolvulus pluricaulis*
- COX-1, 93, 170
- COX-2, 10, 93, 170, 182, 213, 320
- Crataeva magna*. *See* *Crataeva nurvala*
- Crataeva nurvala*, 9i, 157-161
- Crataeva religiosa* var. *nurvala*. *See* *Crataeva nurvala*
- C-Reactive Protein, 165
- Crohn's disease, 33, 35
- Cromoglycate-like activity
 of *Albizia lebbbeck*, 89,
 of *Tylophora indica*, 102
- Curcuma domestica*. *See* *C. longa*
- Curcuma longa*, 10, 163, 170, 319-322, 336
 chemical constituents, 17
 clinical trials, 18, 91-92, 170-171, 320-321, 337-338
 description, 17
 other names, 16, 91, 169
 pharmacology, 17-18, 91, 169-170, 319-320
 safety, 18-19, 92, 322, 338
 traditional use, 17, 91, 169
- Curcuma xanthorrhiza*, 170
- Curcumin 5, 322, 337. *See also* *Curcuma longa*
- Curcuminoids, 10, 17, 18, 91
- Cyclooxygenase, 170, 182, 213
- Cyperus rotundus*, 55-56, 335
- Cytoprotection, 21, 31
- Daily routine (dinacharya), 329
- Dalbergia lanceolaria*, 5, 168, 174
- Darhald. *See* *Berberis aristata*
- Daruharidra. *See* *Berberis aristata*
- Debility, 63, 69, 147, 152, 173, 179
- Demethylwedelolactone, 65
- Dendrite formation, 290
- Dental agents, 329-334
- Dental health, 329, 330-331. *See also* pyorrhea, local anaesthetic and periodontitis
- Deoxyandrographolide, 112, 113
- Depressive illness, 287
- Devadhoopa. *See* *Commiphora wightii*
- Dhanwantari, 2
- Dhanwantari nighantu*, 303
- Diabetes, 229, 230
 main plants for, 231-254
 other plants, 273-275
- Diabetic complications, 230, 275-277

- Diabetic foot, 275
 Diabetic nephropathy. *See* nephropathy, diabetic
 Diabetic neuropathy. *See* neuropathy, diabetic
 Diabetic retinopathy. *See* retinopathy, diabetic
 Diarrhea
 causes, 54
 plants for, 45, 49, 54-58,
 Diet, 119
 Dietary fiber, 256
 Diethyl carbamazine, 116, 117
 Diferuloylmethane. *See* curcumin
 Digestion
 and cancer, 317
 and disease, 13
 and respiratory problems, 85
 and rheumatoid arthritis, 163-164
 ginger for, 14, 181
 Disease and digestion. *See* Ayurveda and digestion
 Diuretics, 151
 Boerhaavia diffusa as, 151-154
 Tribulus terrestris as, 154-155
 Diuretic activity, 81, 151, 152-153, 154
 Dramamine, 39, 40
 Dropsy, 152-153
 Drugs in ancient India,
 absorption, 92
 bioavailability, 4-5
 development of, 2-4
 evaluation, history of, 3-4
 Dryness of throat, *Curcuma longa*, 92
 Dwarakanath C., 131
 Dysmenorrhea, 212
 Dyspepsia, 14, 16, 23-24, 63, 67
 description, 16
 treatment, 16-19, 22, 23-24, 30, 31
 East Indian Walnut tree. *See* *Albizzia lebbek*
Eclipta alba, 62, 65-67
 clinical trial, 29-30, 66
 constituents, 65
 description, 65
 other names, 65
 pharmacology, 65-66
 safety, 66-67
Eclipta erecta. *See* *Eclipta alba*
Eclipta prostrata. *See* *Eclipta alba*
 Eczema, 194, 195
 Azadirachta indica in, 195-196
 Cardiospermum halicacabum in, 197, 198
 Pongamia pinnata in, 200
 Edema, 32, 152
 Ekanayakam, 252. *See also* *Salacia reticulata*
 Elastase inhibition, 34, 164
Eleutherococcus senticosus, 114
 Ellagic acid
 in *Emblica officinalis*, 22
 in *Syzygium cuminii*, 253
 in *Terminalia arjuna*, 121
 in *Terminalia belerica*, 58
 in *Terminalia chebula*, 49
 Embelic myrobalan. *See* *Emblica officinalis*
Emblica officinalis, 1i, 10, 22-25, 305.
 See also under triphala
 clinical trials, 23-24, 143, 307-308
 constituents, 22-23
 description, 22
 other names, 22, 306
 pharmacology, 23, 143, 307
 safety, 24-25
 traditional use, 22, 306
 Emblicanin A, B, 23, 307
 Emetic swallow-wort. *See* *Tylophora indica*
 Endothelial function, 122
Entamoeba histolytica, 15, 55
 Eosinophil count, 89, 90, 93, 103, 104, 116, 117
 Epicatechin, 88, 226, 246
 Erand. *See* *Ricinus communis* and castor
 Eranda. *See* *Ricinus communis* and castor
Escherichia coli, 54, 57, 70
 Essentiale, 78
Eugenia cuminii. *See* *Syzygium cuminii*
Eugenia jambolana, 5, 230, 247. *See also* *Syzygium cuminii*
 Eugenol, 93
 Expectorant, 17,
 Adhatoda vasica, 86, 87
 Boswellia serrata, 90,
 Curcuma longa, 17

Expectorant (*continued*)

- Inula racemosa*, 126
- Ipecacuanha, 103
- Ocimum sanctum*, 93
- Solanum xanthocarpum*, 97, 98
- Tylophora indica*, 101

Fenugreek. *See Trigonella foenum-graecum*

Ferulic acid, 253

Fever, 63, 111, 113, 114

Five-leaved chaste tree. *See Vitex negundo*

Flavonoids,

- in *Adhatoda vasica*, 87
- in *Aloe barbadensis*, 213
- in *Andrographis paniculata*, 63
- in *Azadirachta indica*, 231, 232
- in *Bacopa monnieri*, 281
- in *Cardiospermum halicacabum*, 198
- in *Crataeva nurvala*, 157, 158
- in *Eclipta alba*, 65
- in *Embllica officinalis*, 143, 308
- in fenugreek, 256
- in *Glycyrrhiza glabra*, 31
- hypoglycemic activity of, 232
- in *Musa sapientum*, 25
- in *Ocimum sanctum*, 93
- in *Phyllanthus amarus*, 77
- in *Pongamia pinnata*, 199
- in *Psoralea corylifolia*, 204, 205
- in *Pterocarpus marsupium*, 245, 246
- in *Saraca asoca*, 226
- in *Semecarpus anacardium*, 172
- in *Terminalia arjuna*, 121
- in *Terminalia chebula*, 49
- in *Tinospora cordifolia*, 69
- in *Tribulus terrestris*, 154
- in *Tylophora indica*, 101
- in *Vitex negundo*, 176

Follicular eczema, 204, 206

Forskolin, 145, 340

Fr A, clinical trial, 134-135, 136

Fracture healing, 219-221.

Free radical damage, 305, 306, 307

Free radical scavenging activity, 10, 31, 254, 281, 290, 306

Friedelin

- in *Albizzia lebbbeck*, 88
- in *Crataeva nurvala*, 158
- in *Terminalia arjuna*, 121

Frozen shoulder, 5, 168, 174

Fructose-1,6-bisphosphatase, 235

FXR Antagonist Receptor, 133

GABA, 284, 288, 289

Galactagogue, 223, 224, 256

Asparagus racemosus as, 223-224

Gallic acid, 22, 49, 58, 93, 253, 254, 299

Gamma-amino butyric acid. *See* GABA

Gastric emptying, 22, 41, 49

Gastric irritation, 15, 18, 69, 178

Gastrointestinal agents, 13-60

Gastrointestinal stimulant drugs in RA, 164, 181, 182

General debility, 63, 152

Geraniin, 78

Geriatric, 233

Ghi-kuvar. *See Aloe barbadensis; Aloe vera*Ghrita kumari. *See Aloe barbadensis; Aloe vera**Giardia*, 15, 54, 55, 57Giloe. *See Tinospora cordifolia*Ginger, 85. *See also Zingiber officinale*

Gingerols, 14, 182

Gingival inflammation index, 333

Gingivitis, 329, 330

Glaucoma, 333, 336, 340

Glibenclamide, 238, 239, 254

Glioblastoma, 37, 318, 319

Glucose-6-phosphatase, 236, 254

Glycoprotein, 212, 213, 238

Glycosaminoglycan synthesis, 212, 214

Glycosylated hemoglobin, 239, 244, 249, 252

Glycyrrhiza glabra, 29, 30-32, 223, 334, 338

clinical trials, 31, 336

constituents, 31

safety, 31-32

use, 31

- Glycyrrhizin, 31, 32
 Gokhru. *See Tribulus terrestris*
 Gokshura. *See Tribulus terrestris*
 Gourakh. *See Dalbergia lanceolaria*
 Grape seed extract, 10
 Greater triad, 2
 Gridharasi. *See sciatica*
 Guduchi. *See Tinospora cordifolia*
 Guggul and Katibasti, 168
 Guggul, 133-137, 166-169. *See also*
 Commiphora wightii;
 Commiphora mukul
 Guggul, effect of age of sample, 132,
 138
 Guggulipid, 135-136, 137
 Guggulu. *See Commiphora wightii*;
 Commiphora mukul
 Gurmali. *See Coleus forskohlii*
 Gurmarin, 237
Gymnema sylvestre, 11i, 5, 232,
 237-240, 246
 clinical trials, 238-240
 constituents, 237
 other names, 237
 pharmacology, 237-238
 safety, 240
 use, 237
Gymnema sylvestre and *Eugenia*
 jambolana, 5, 253, 255
 Gymnemic acid I-III, 238
 Gymnemic acid IV, 237, 238
 Gymnemic acids, 237, 238
 Gymnemic acids A-D, 239
 Gynecological agents, 223-227

 Haldi. *See Curcuma longa*
 Halitosis, 333
 Harad. *See Terminalia chebula*
 Harar. *See Terminalia chebula*
 Haridra. *See Curcuma longa*
 Haritaki. *See also Terminalia chebula*
 HBsAg binding, 9, 80
 and *Eclipta alba*, 66
 and *Phyllanthus amarus*, 77-78
 and picroliv, 80
 Heart block, 120
 Heart disease, 5
 Heart disease in Ayurveda. *See* Caraka
 and *Caraka samhita*

Helicobacter pylori, 20, 31
 Hemoglobin,
 and *Centella asiatica*, 312
 and *Embllica officinalis*, 307
 and ginger, 15
 and *Withania somnifera*, 181,
 308, 309
 Hepatitis B, 76
 Hepatitis B surface antigen. *See* HBsAg
 Hepatocellular jaundice, *Picrorhiza*
 kurroa, 68
 Hepatoprotective agents, 61-83. *See*
 also antiviral activity and viral
 hepatitis
 Andrographis paniculata, 63-64
 Boerhaavia diffusa, 81
 Eclipta alba, 65-67
 Phyllanthus amarus, 76-78
 Picrorhiza kurroa, 67-69
 scientific studies on, 62
 Tinospora cordifolia, 69-71
 Herb, time of collection. *See under*
 Caraka samhita
Herpes genitalis, 200
Herpestis monniera. *See Bacopa*
 monnieri
Holarrhena antidysentrica, 56-57
 Holy basil, 193. *See also Ocimum*
 sanctum
 Humoral immune response, 102, 195,
 313, 322
Hydrocotyle asiatica. *See Centella*
 asiatica
 4-Hydroxyisoleucine, 256, 257
 5-Hydroxytryptamine, 25, 180, 284,
 289, 299
 Hyperacidity, 16, 20, 21, 29, 37, 91
Hypericum perforatum, 127
 Hyperlipidemic effect, 236
 Hyperproliferation, 207, 208
 Hypersensitivity reaction, 215
 Hypertension, 144-145. *See also* blood
 pressure
 Hypertension, stress related and
 Ocimum sanctum, 93-94
 Hypertrophy of scars, 215, 218
 Hypocholesterolemic effect,
 Commiphora wightii,
 132-133

- Hypolipidemic plants, 4, 8, 9, 57, 100
Commiphora wightii, 131-138
Emblica officinalis, 143
Terminalia arjuna, 125
Trigonella foenum graecum, 138-139, 257, 258
- Hypophyllanthin in *Phyllanthus amarus*, 77
- ICMR, 7, 245
- Idiopathic inflammatory orbital pseudotumors, 337
- Ischemic heart disease, 120, 122, 126, 133, 137
- Immune stimulation, 305
- Immune suppression, 70, 102
- Immunomodulatory activity
 of *Albizia lebeck*, 89
 of *Aloe barbadensis*, 213
 of *andrographolide*, 112
 of *Boerhaavia diffusa*, 152
 of neem, 195
 of *Psoralea corylifolia* seeds, 205
 of *Tinospora cordifolia*, 313
 of *Withania somnifera*, 179
- Immunostimulant activity
 and *Aloe*, 212
 and *Centella asiatica*, 316
 and *Curcuma longa*, 169
 and *Piper longum*, 85
 and *Tinospora cordifolia*, 69, 313-315, 322
 and *Withania somnifera*, 308
- Increased protein synthesis, 64, 68, 214, 288
- Indian aloe. *See Aloe barbadensis*; *Aloe vera*
- Indian bdellium. *See Commiphora wightii*; *Commiphora mukul*
- Indian cassia lignea. *See Cinnamomum tamala*
- Indian Council for Research in Indian Medicine, 7
- Indian Council of Medical Research. *See ICMR*
- Indian frankincense. *See Boswellia serrata*
- Indian ginseng, 179
- Indian Herbal Pharmacopoeia
Adhatoda vasica, 87
- Indian Herbal Pharmacopoeia
 (continued)
Aegle marmelos, 54, 55
Andrographis paniculata, 63, 64
Bacopa monnieri, 280
Boerhaavia diffusa, 81-82, 152
Celastrus paniculatus, 286
Centella asiatica, 284
Commiphora wightii, 132
Crataeva nurvala, 157
Curcuma longa, 169
Eclipta alba, 65
Emblica officinalis, 22
Glycyrrhiza glabra, 31
Nardostachys jatamansi, 302
Ocimum sanctum, 93
Phyllanthus amarus, 77
Picrorhiza kurroa, 67
Piper longum, 95
Plantago ovata, 45
Ricinus communis, 47
Solanum xanthocarpum, 97
Terminalia belerica, 57, 100
Terminalia chebula, 49
Tinospora cordifolia, 69, 175
Tribulus terrestris, 154
Withania somnifera, 179
Zingiber officinale, 14, 182
- Indian ipecacuanha. *See Tylophora indica*
- Indian long pepper. *See Piper longum*
- Indian madder. *See Rubia cordifolia*
- Indian olibanum. *See Boswellia serrata*
- Indian pennywort. *See Centella asiatica*
- Indian Pharmacopoeia, Babchi ointment, Application of
Psoralea, 206
- Indian senna. *See Cassia angustifolia and senna*
- Indian substitute for insulin, 234
- Indian valerian. *See Valeriana wallichii*
- Indra, 2
- Influenza epidemic and *Andrographis paniculata*, 111, 114
- Inji. *See Zingiber officinale*
- Intellect tree. *See Celastrus paniculatus*
- Interferon alpha 2b, 316
- Inula racemosa* 5, 125-128

- Inula racemosa* and *C mukul*, 126
Inula racemosa, *C mukul* and *Bacopa monnieri*, 5, 127
Inula racemosa, *C mukul*, *Centella asiatica* and *Hypericum perforatum*, 127-128
Inulin, 126
Iridoid glycosides in *Vitex negundo*, 176
Irritable bowel syndrome
 and *Aegle marmelos*, 55
 and *Plantago ovata*, 46,47
 and turmeric, 18
Isabgol. *See Plantago ovata*
Isapghul(a). *See also Plantago ovata*
Isapghulla, 55
Ischemic cardiomyopathy and
 Terminalia arjuna, 124
Ishappukol. *See Plantago ovata*
Islets of Langerhans, 237-238
Isoalantolactone, 126
Isoliquiritigenin, 31
Isoprenaline, 103
Isopsoralen, 204, 205
- Jam. *See Syzygium cuminii*
Jaman. *See Syzygium cuminii*
Jambu. *See Syzygium cuminii*
Jamun. *See Syzygium cuminii*
Jatamanshi. *See Nardostachys jatamansi*
Jatrorhizine in *Tinospora cordifolia*, 69
Jivika on wound healing, 211
Justicia adhatoda. *See Adhatoda vasica*
Jyotishmati. *See Celastrus paniculatus*
- Kadali. *See Musa sapientum*
Kaddukai. *See Terminalia chebula*
Kaempferol in *Tylophora indica*, 101
Kaffir potato. *See Coleus forskohlii*
Kalmegh. *See Andrographis paniculata*
Kampavata. *See Parkinson's disease*
Kan jang, 114
Kandankattiri. *See Solanum xanthocarpum*
Kantakari. *See Solanum xanthocarpum*
Karabella. *See Momordica charantia*
Karanjin, 199
Karasalanganni. *See Eclipta alba*
Karela. *See Momordica charantia*
Kasyapa Samhita, 3
Kateli. *See Solanum xanthocarpum*
Kattalai. *See Aloe barbadensis*; *Aloe vera*
Katuka. *See Picrorhiza kurroa*
Katukarogini. *See Picrorhiza kurroa*
Katurohini. *See Picrorhiza kurroa*
Keelanelli. *See Phyllanthus amarus*
Kela. *See Musa sapientum*
Kesharaj. *See Eclipta alba*
11-Keto- β -boswellic acid, 34
Kidney problems, 31, 151-161
Kirata. *See Andrographis paniculata*
Korai. *See Cyperus rotundus*
Koranti. *See Salacia reticulata*;
 S. oblonga
Koreti-jar. *See Cyperus rotundus*
Kotak, G.B., 101
Kotalanol, 250, 251
Kumari. *See Aloe barbadensis*;
 Aloe vera
Kurchee. *See Holarrhena antidysentrica*
Kurchi. *See Holarrhena antidysentrica*
Kutaja. *See Holarrhena antidysentrica*
Kutajarista, 57
Kutki. *See Picrorhiza kurroa*
Kutkin, 53, 68
Kutkoside, 53, 67
Kutkoside I, 68
- Lactate dehydrogenase, 236
Lactobacillus, 330, 331
Land Calotrops. *See Tribulus terrestris*
Laryngitis, 95
Laxative effect, 237, 245
 and *Aegle marmelos*, 54
 and *Boerhaavia diffusa*, 152, 153
 and *Embolia officinalis*, 24, 25,
 and *Terminalia belerica* 57, 100, 101
Laxatives. *See also* triphala and
 Ayurveda, 43
 Cassia angustifolia, 43-45
 Picrorhiza kurroa, 53, 69
 Plantago ovata, 45-47
 Ricinus communis, 47-50
 Terminalia chebula, 49-50
L-DOPA in *Mucuna pruriens*, 298-299

- Leucas aspera, 193
 Leucoanthocyanidins, 25, 121
 Leukoderma, 204.
 and *Psoralea corylifolia*, 204-205
 Leukorrhea, 225
 Leukotrienes, 33, 35,
 and disease, 9, 90, 164, 317
 and inflammation, 33, 35
 in asthma, 90
 in tumors, 318
 Leukotriene synthesis enhancer, 36
 Leukotriene synthesis inhibition
 and *Boswellia serrata*, 9, 34
 and 11-AKBA, 34
 and boswellic acids, 33, 34, 35, 164
 Licorice. *See Glycyrrhiza glabra*
 Lifestyle, 119
 Lignans
 in *Boerhaavia diffusa*, 152
 in *Phyllanthus amarus*, 77
 in *Tinospora cordifolia*, 69
 Liminoids, 231
 Lipoprotein lipase, 236
 Lipoyxygenase, 170, 182
 5-Lipoxygenase inhibition, 9, 30, 34,
 36, 66
 Liquiritigenin, 31, 246, 247
 Liquorice. *See Glycyrrhiza glabra*
 Liver cell regeneration, 9, 65, 82
 Liver disorders, 61-62
 Local anaesthetic, 333, 334
 Long pepper. *See Piper longum*
Luffa echinata, 80-81
 Lupeol
 in *Aloe barbadensis*, 212
 in *Coccinia grandis*, 234
 in *Crataeva nurvala*, 157
 in *Gymnema sylvestre*, 237
 in *Holarrhena antidysenterica*, 56
 in *Wrightia tinctoria*, 209
 Luteolin, 93, 176, 198

 Macrophages, 70, 112, 309, 313, 314,
 322
 Madecassic acid, 147, 214
 Madecassoside, 147
 Madhudarvyadi, 337
 Maharasanadi kwath, 183
 Mahatriphaladi ghrita, 335

 Maishaki gukkal. *See Commiphora*
 wightii; *Commiphora mukul*
 Majit. *See Rubia cordifolia*
 Makandi. *See Coleus forskohlii*
 Malabsorption of fat, *Cyperus*
 rotundus 56
 Malabsorption syndrome, 13-15, 181
 Malignant obstructive jaundice and
 Tinospora cordifolia, 70-71
 Malkanguni oil, 286
 Malkanguni. *See Celastrus paniculatus*
 Mandukaparni. *See Centella asiatica*
Mangifera indica, 330
 Mangiferin, 250, 251
 Manjal. *See Curcuma longa*
 Manji. *See Rubia cordifolia*
 Manjishta. *See Rubia cordifolia*
 Manjitti. *See Rubia cordifolia*
 Mannose-6-phosphate, 212, 213
 Maralingam. *See Crataeva nurvala*
 Maramanjal. *See Berberis aristata*
 Markand. *See Cassia angustifolia*
 Marking nut. *See Semecarpus*
 anacardium
 Marsupin, 246, 247
 Mast cell degranulation and *Albizia*
 lebbek, 89, 102
 Mayini. *See Coleus forskohlii*
 Medhya rasayana, 146, 280, 283, 288,
 289, 305. *See also* individual
 plants
Melia azadirachta. *See Azadirachta*
 indica
Melia azedarach, 233
 Memory and learning enhancers, 280
 and plants, 280-291
 Menorrhagia,
 description, 226
 and *Saraca asoca*, 226-227
 Mental fatigue, reduction by *Withania*
 somnifera, 291
 Mental rejuvenation. *See* medhya
 rasayana
 Mental rejuvenators, 280
 Mesalazine, 35, 36
Mesua ferrea, 223
 Methi. *See Trigonella foenum-graecum*
 Methika. *See Trigonella*
 foenum-graecum

- 8-Methoxypsoralen, 41
 Metoclopramide, 22, 41, 49
 Metromenorrhagia, 226
 Milk decoction of *Terminalia arjuna*, 120
Mimosa pudica in dysfunctional uterine bleeding, 227
Momordica charantia, 230, 240-245
 clinical trials, 243-245
 constituents, 241
 description, 240-241
 other names, 240
 pharmacology, 241-243
 safety, 245
 use 241.
 Momordicin Ic, 241, 243
 Monodemethoxycurcumin. *See* curcumin I, 17
 Morning stiffness, 164, 165, 167, 170, 183
 Moth. *See* *Cyperus rotundus*
 Mucilage
 in *Plantago ovata*, 45
 in *Trigonella foenum graecum*, 256
 Mucosal resistance, 20, 21, 25
Mucuna pruriens, 12i, 298-300
Mucuna prurita. *See* *Mucuna pruriens*
Mukkarete. *See* *Boerhaavia diffusa*
Mulethi. *See* *Glycyrrhiza glabra*
Murraya koenigi, 328
Musa sapientum L var. *paradisiaca*, 25-26
 Musta. *See* *Cyperus rotundus*
 Mustaka. *See* *Cyperus rotundus*
 Mutagenic activity, 221
 Mutagenic potential, 15, 39, 221
 Mutagenic role, anthraquinones, 45
 Mutagenicity, 39, 40, 252
 Mutha. *See* *Cyperus rotundus*
 Mutra kricchara. *See* urinary tract infections

Nardostachys jatamansi, 301-302
 Nayppalai. *See* *Tylophora indica*
Neem, 193. *See also* *Azadirachta indica*
 Nelli. *See* *Emblica officinalis*
 Nephritis, parenchymatous, 152
 Nephropathy, diabetic, 230, 238
 Nephrotic syndrome and *Boerhaavia diffusa*, 153

Nerunji. *See* *Tribulus terrestris*
 Neurodermatitis, 194, 198
 Neuropathy, diabetic, 230, 238, 275, 276
 Neurotransmitter levels, 284
 Neutropenia reduction with *Tinospora cordifolia*, 322-323
 New York Heart Association. *See* NYHA
 Nilavari. *See* *Cassia angustifolia*
 Nilavemb. *See* *Andrographis paniculata*
 Nimb. *See* *Azadirachta indica* and *neem*
 Nimba. *See* *Azadirachta indica* and *neem*
 Nimbidin, 196, 208
 Nimbidin-T, 330
 Nirgundi. *See* *Vitex negundo*
 Nirparami. *See* *Bacopa monnieri*
 NO synthesis inhibition
 and andrographolide, 112
 and [6]-gingerol, 182
 Nochi. *See* *Vitex negundo*
 Nonspecific dermatitis, 210
 Norwedelolactone. *See* demethylwedelolactone
 Nut grass. *See* *Cyperus rotundus*
 NYHA, 123, 124

 Obesity, 9, 123, 131, 132, 133, 138
Ocimum sanctum, 10, 92-94, 111, 232, 330
 clinical trials, 93-94, 115, 116-117
 constituents, 93
 description, 92-93
 other names, 92
 pharmacology, 93
 safety, 94
 use, 93, 94, 328
Ocimum sanctum and *Cissus quadrangularis*, 221
Ocimum sanctum. *See also* holy basil
Ocimum tenuiflorum. *See* *Ocimum sanctum*
 Odansetron, 41
 Oleonic acid-3-O-glucuronide, 241-242
 Ophthalmic conditions, painful, 340
 Ophthalmological agents, 335-340
 Oral leucoplakia, 321
 Oral submucous fibrosis, 320-321

- Oriental cashew. *See Semecarpus anacardium*
- Osteoarthritis, 167-168, 170
- Osteoarthritis, *Commiphora mukul*, 167
- Osteoarthritis in dog, 170
- Osteoporosis, 219, 220
- Oxytocic activity, 21, 224, 226, 227
- PAF mediated inflammatory/allergic response inhibition, 87, 112
- Palmitine, 69
- Panchakarma treatment, 181
- Paracetamol, 113, 114
- Parakeratosis, 209
- Paralysis, residual, 94
- Parangi sambrani. *See Boswellia serrata*
- Parinamshool, 20
- Parkinson's disease, 298
and *Mucuna pruriens*, 298-300
- Pavakka. *See Momordica charantia*
- Pectin
in *Aegle marmelos*, 54
in *Aloe barabadensis*, 212
in *Coccinia grandis*, 234, 235
in *Embolica officinalis*, 22
in *Musa sapientum*, 25, 26
- Pediatric, 233
- Pepper. *See Piper nigrum*
- Peptic ulcer,
cause of, 20
plants for, 20-26, 29-32
- Periodontitis, 329, 330, 334
- Peristalsis, 14, 44, 45
- Persian lilac. *See Melia azedarach*
- Phagocytic activity, 22, 25, 50, 70, 102
- Pharyngotonsillitis, 113
- Phosphatidyl choline, 26, 29
- Phospholipase A2 inhibitor, 66, 198
- Phyllanthin in *Phyllanthus amarus*, 77
- Phyllanthus amarus*, 51, 62, 76-78, 274-275
clinical trials, 77-78, 274-275
constituents, 77
description, 77
history of use, 77
identity 76
other names 76, 274
pharmacology, 77
safety, 78
- Phyllanthus amarus* and *Picrorhiza kurroa*. *See Picrorhiza kurroa*
- Phyllanthus emblica*, 252. *See also Emblica officinalis*
- Phyllanthus fraternus*, 76
- Phyllanthus niruri*, 76
- Picroliv, 10, 53, 68, 80
- Picrorhiza kurroa*, 10, 53, 62, 67-69, 80
as laxative, 53
clinical trials, 53, 68, 80
constituents, 53, 67
other names, 53, 67
pharmacology, 53, 67-68, 80
use, 67
description, 67
safety, 68-69
- Picrorhiza kurroa* and *Phyllanthus amarus*, 80
- Picroside I, 53, 67, 68
- P-insulin, 241, 244, 245
- Piper longum*, 4, 8, 85, 94-97
clinical trials, 95-96
constituents, 95
description, 95
other names, 94
pharmacology, 95
uses, 94-95
- Piper nigrum* in trikatu, 4
- Piperine, 4, 5, 95, 170
- Pipltartine, cough reflex suppression, 95
- Pipli. *See Piper longum*
- Pippali. *See Piper longum*
- Pitika. *See Salacia reticulata*
- Pityriasis versicolor*, 193, 200
- Plantago ovata*, 45-47
- Plantago. *See Plantago ovata*
- Plantain. *See Musa sapientum*
- Plaque, 329, 330
- Platelet aggregation, 15, 133, 137, 167, 182
- Poison antidote, 63, 88
- Pokharmoola. *See Inula racemosa*
- Pongamia pinnata*, 199-201
- Ponkoranti. *See Salacia reticulata* and *S. oblonga*
- Positive inotropic action, ginger, 15
- Postoperative inflammation (hernia/hydrocele), curcumin, 171

- Pregnancy
 and *Adhatoda vasica*, 88
 and *Asparagus racemosus*, 20
 and ginger, 15, 39
 and guggul, 137
 and *Momordica charantia*, 245
 and *Salacia reticulata*, 253
- Pregnant women and *Nardostachys jatamansi*, 302
- Prochlorperazine, 41
- Prolactin levels, 223, 224
- Prostate. *See* benign prostatic enlargement
- Psoralea corylifolia*, 204-206
- Psoralen, 204, 205
- Psoriasis, 194, 207-208
 and *Aloe vera*, 208
 and *Centella asiatica*, 208
 and *Wrightia tinctoria*, 208-210
- Psoriatic arthritis, Aurinofin, 167, 175
- Psyllium and senna, 44, 46
- Psyllium, 43. *See also* *Plantago ovata*
- Pterocarpus marsupium*, 245-249
 clinical trials, 247-249
 constituents, 246
 description, 245
 other names, 245
 pharmacology, 246-247
 safety, 249
 traditional use, 245-246
- Pterostilbene, 246, 247
- Pterosupin, 246, 247
- Punarnava, 310. *See also* *Boerhaavia diffusa*
- Punarnavoside in *Boerhaavia diffusa*, 152
- Puncture vine. *See* *Tribulus terrestris*
- Pushkara. *See* *Inula racemosa*
- Pushkaramoola. *See* *Inula racemosa*
- Pyelonephritis, 152
- Pyorrhea, 87, 329, 332, 333, 334
- Quality of life, 314, 315
- Quercetin
 in *Cardiospermum halicacabum*, 198
 in *Crataeva nurvala*, 158
 in *Syzygium cumini*, 253
 in *Tylophora indica*, 101
- Raj Nighantu*, 145
- Raloxifene, 220
- Rasayana, 10, 280, 283, 305-326.
See also Cancer therapy, immunostimulant effects and tonic/antiaging effects
Asparagus racemosus as, 305
Boerhaavia diffusa as, 152
Centella asiatica as, 312, 316
 description, 306
Embllica officinalis as, 305, 306-308
 Naimittika rasayana, 174
Piper longum as, 305
Semecarpus anacardium as, 172
Tinospora cordifolia as, 305, 313-315
Withania somnifera as, 179, 308-310
- Rasonadi quath, 178
- Rejuvenation, 43
- Respiratory problems and digestion.
See digestion
- Respiratory stimulant, *Piper longum*, 95
- Respiratory tract drugs, 85, 86-117
- Retinopathy, diabetic, 230
- Rhein an throne, 44
- Rheumatoid arthritis,
 cause of, 163-164
 plants for, *see* anti-rheumatic agents
- Rhinorrhea, 80-81
- Ricinoleic acid, 48
- Ricinus communis*, 47-48
- Rifampicin, 4
- Ringworm, 193, 194, 195-196, 200
- Rosmarinic acid, 10, 93
- Rotenoids in *Boerhaavia diffusa*, 152
- Rubia cordifolia*, 275-276, 336, 340
- Sacred basil. *See* *Ocimum sanctum*
- Salacia chinensis*. *See* *S. prnoides*
- Salacia fruticosa*, 250, 251
- Salacia latifolia*. *See* *S. prnoides*
- Salacia macrosperma*, 250, 251
- Salacia oblonga*, 249, 250, 251, 253
- Salacia prnoides*, 249, 250-251, 252
- Salacia prnoides* and *Strychnos potatorum*, 252
- Salacia reticulata*, 249, 250, 251-252, 252-253

- Salacia* spp., 249-253
 clinical trials, 251
 constituents, 250
 description, 250
 other names, 249-250
 pharmacology, 250-251
 safety, 252-253
 uses, 250
- Salai guggul. *See Boswellia serrata*
- Sallaki. *See Boswellia serrata*
- Salmonella typhimurium*, 221
- Sambhalu. *See Vitex negundo*
- Sandhigatavata. *See osteoarthritis*
- Sankahul. *See Convolvulus pluricaulis*
- Saponins
 in *Albizzia lebbeck*, 88, 89
 in *Asparagus racemosus*, 20-21
 in *Centella asiatica*, 147
 in *Solanum xanthocarpum*, 98
 in *Tribulus terrestris*, 154
 in *Trigonella foenum graecum*, 138
- Saptrangi. *See Salacia prinoidea*
- Saraca asoca*, 223, 226-227
- Satavari. *See Asparagus racemosus*
- Satyavati, G.V., 131
- Saussurea lappa*, 248
- Scabies, 194, 195, 196, 199
- Sciatica, 5, 95, 168, 174, 178
- Scientific investigation. *See scientific research*
- Scientific research, 7-8
 trends arising from, 9-10
- Sedative, 284, 286, 301
- Sedative plants, 301-304
- Semecarpus anacardium*, 5, 163, 168, 171-175. *See also amrit bhallatka*
- Senkottei. *See Semecarpus anacardium*
- Senna, 43, 53. *See also Cassia angustifolia*
- Senna and psyllium. *See psyllium*
- Sennoside A and B, 44, 45, 48
- Sennoside A in *Terminalia chebula*, 49
- Sephadex, 8
- Shankapuspi. *See Convolvulus pluricaulis*
- Shatavari. *See Asparagus racemosus*
- Shatavarin I, 224
- Shatavarin IV, 21
- Shigella*, 55
- Shingles zoster*, 193, 200
- Shivpuri, D.N., 101
- Shogaols, 14
- Sida cordifolia*, 111, 115, 276
- Sida rhombifolia*, 111, 115
- Sida vernoncaefolia*, 111, 115-116
- Siddha medicine, 209
- Side effects 255, 299, 300
Aconitum, 4
Andrographis paniculata, 64
Bacosides A and B, 283
Boswellia serrata, 37, 91, 319
Commiphora mukul, 4, 132, 134, 137
Curcuma longa, 18-19, 92
Emblica officinalis, 25
Glycyrrhiza glabra, 31-32
Holarrhena antidysentrica, 57
Inula racemosa, 128
Mucuna pruriens, 299-300
Ocimum sanctum, 94
Picrorhiza kurroa, 69
Piper longum, 97
Plantago ovata, 47
Psoralea corylifolia, 205, 206
Pterocarpus marsupium, 249
Ricinus communis, 48
Semecarpus anacardium, 173, 175
Solanum xanthocarpum, 100
Syzygium cumini, 255
Terminalia arjuna, 125
Trigonella foenum graecum, 258
Tylophora indica, 102, 104
Zingiber officinale, 184
- Sindal. *See Tinospora cordifolia*
- Sinduwar. *See Vitex negundo*
- Sinusitis, 112
- Siris. *See Albizzia lebbeck*
- Sirisha. *See Albizzia lebbeck*
- Sitoidosides, 60, 179, 289, 290, 308
- Skin cancer, 318
- Skin diseases, 194
 and *Aloe vera*, 208
 and *Azadirachta indica*, 194-196
 and *Cadiospermum haliacabum*, 197-199
 and *Centella asiatica*, 208
 and *Pongamia pinnata*, 199-201
 and *Psoralea corylifolia*, 204-206
 and *Wrightia tinctoria*, 208-210

- Skin disorders, 193-194
 Skin irritation, 37, 206, 214
 Skin itching, 207
 Skin regeneration, 212
 Skin and trauma care agents, 193-221
 Solamargine, 97
Solanum surratense. *See* *Solanum xanthocarpum*
Solanum trilobatum, 85, 99
Solanum xanthocarpum, 85, 97-100
 Solasodine, 97, 100
 Sonamukhi. *See* *Cassia angustifolia*
Staphylococcus aureus, 205, 206
 Sterols
 in *Aegle marmelos*, 54
 in *Aloe barbadensis*, 212
 in *Bacopa monnieri*, 281
 in *Borhaavia diffusa*, 152
 in *Cardiospermum halicacabum*, 198
 in *Commiphora mukul*, 132
 in *Crataeva nurvala*, 157
 in *Ocimum sanctum*, 93
 in *Phyllanthus amarus*, 77
 in *Pongamia pinnata*, 199
 in *Saraca asoca*, 226
 in *Solanum xanthocarpum*, 97
 in *Terminalia arjuna*, 101
 in *Tribulus terrestris*, 154
 in *Trigonella foenum graecum*, 256
 in *Tylophora indica*, 101
 Stone apple. *See* *Aegle marmelos*
Streptococcus faecalis, 330
Streptococcus mutans, 329, 330, 331
Strychnos nux vomica, 196
Strychnos potatorum, 252
 Students and *Nardostachys jatamansi*, 302
 Sukku. *See* *Zingiber officinale*
 Sulfasalazine, 36, 37
 Sunth. *See* *Zingiber officinale*
 Sunthi. *See* *Zingiber officinale*
 Sushruta 2, 302
 Curcuma longa, 169
 heart disease, 119,
 Ricinus communis, 47
 Solanum xanthocarpum, 97
 Terminalia arjuna, 120
 Sushruta Samhita
 atherosclerosis, 131, 132
 Commiphora mukul, 132
 diabetes, 229
 fractures in, 219
 guggul resin, age of, 132, 138
 Nardostachys jatamansi, 302
 obesity, 131, 132, 138
 Terminalia arjuna, 121
 wound healing in, 211
 Sutras, 2
 Synerges(t)ic activity, 15, 233, 245
 Synergy, 4, 5
 Syringin, 69, 313
Syzygium cumini, 253-255

 Tagara. *See* *Valeriana wallichii*
 Takkari. *See* *Clerodendron phlomidis*
 Talishapattiri. *See* *Cinnamomum tamala*
 Tamaka swasa. *See* bronchial asthma
 Tamalaki. *See* *Phyllanthus amarus*
 Tamalapatra. *See* *Cinnamomum tamala*
 Tannins, 8, 226
 in *Albizzia lebbek*, 88
 in *Aloe barbadensis*, 212
 in *Cardiospermum halicacabum*, 198
 in *Emblica officinalis*, 22, 307
 in *Ocimum sanctum*, 93
 in *Phyllanthus amarus*, 77
 in *Terminalia arjuna*, 121
 in *Terminalia chebula*, 49
 in *Tribulus terrestris*, 154
 Tanri. *See* *Terminalia bellerica*
 Tarkaari. *See* *Clerodendron phlomidis*
 Tejpat. *See* *Cinnamomum tamala*
 Tejpatra. *See* *Cinnamomum tamala*
Terminalia arjuna, 6i, 120-125
 clinical trials, 122-125
 constituents, 121
 description, 120-121
 other names, 120
 pharmacology, 121-122
 safety, 125
 use, 120, 121

- Terminalia belerica*, 57-58, 100-101.
 See also triphala
 clinical studies, 58, 100-101, 116
 constituents, 58
 description, 57
 other names, 57
 pharmacology, 58
 safety, 58
 traditional use, 57
- Terminalia chebula*, 49-50. *See also* triphala
- Terpene glycosides, 49, 121
- Terrestrosins, *Tribulus terrestris*, 154
- Testosterone binding, 40
- Tetrahydroamentoflavone, 172
- 3, 3', 4, 4'-Tetrahydroxybiphenyl, 219
- Tetranortriterpenoids, 231
- Thaludalai. *See* *Clerodendron phlomidis*
- Thromboxane A2 synthase, 213
- Thromboxane synthase, 182
- Thulasi. *See* *Ocimum sanctum*
- Thyme leaved gratiola. *See* *Bacopa monnieri*
- Thyroid stimulatory activity, 133
- Tinnevely senna. *See* *Cassia angustifolia* and senna
- Tinospora cordifolia*, 4i, 62, 69-71, 163, 305, 310, 313-315
 antiaging tonic, 310
 arthritis, 175-176
 asthma, 315
 constituents, 69, 313
 description, 69, 175
 in cancer therapy, 323
 obstructive jaundice, 70-71
 other names 69, 313
 pharmacology, 70, 175, 313, 322-323
 safety, 71
 traditional use, 69, 175
 tuberculosis, 313-314
- Tinospora cordifolia* and *Zingiber officinale*, 182-183, 184
- Tinospora glabra*. *See* *Tinospora cordifolia*
- Tippali. *See* *Piper longum*
- Tolbutamide, 239, 248, 250, 251, 274
- Tonic, *Curcuma longa* in IHP, 169
- Tonic/antiaging effects, 306
 and *Embllica officinalis*, 306-308
 and *Centella asiatica*, 312
 and *Tinospora cordifolia*, 310
 and *Withania somnifera*, 308-310
- Topoisomerase I and II, 318
- Toxicity
 Harmane, Norharmane, 155
 Neem oil, 233-234
 Pongamia pinnata, 200-201
 Semecarpus anacardium, 174-175
 Tribulus terrestris, 155
- Trailing Eclipta. *See* *Eclipta alba*
- Tranquilizing action
 and *Celastrus paniculatus*, 286
 and *Centella asiatica*, 283
 and *Convolvulus pluricaulis*, 288
 and *Nardostachys jatamansi*, 302
- Tribulus terrestris*, 151, 154-155,
Trigonella foenum-graecum, 138-139, 256-259
 clinical trials, 139, 257-258
 constituents, 256
 description, 256
 other names, 138, 256
 pharmacology, 138-139, 256-257
 safety, 258-259
 uses, 256
- Trigonelline, 256, 257
- Trikatu, 4, 5, 14
- Triphala, 43, 49, 100, 132
 in Mahatriphaladi Ghrita, 335-336
 in periodontitis, 332
 in "purification" of guggul, 4, 132
 and *Salacia prinoidea*, 252
- Triricinolein, 47-48
- Triterpenes
 in *Centella asiatica*, 214
 in *Cissus quadrangularis*, 219
 in *Crataeva nurvala*, 158
 in *Holarrhena antidysenterica*, 56
 in *Pongamia pinnata*, 199
 in *Terminalia arjuna*, 121
- Tropical pulmonary eosinophilia,
Albizia lebbek, 90, 116
Curcuma longa, 92
Ocimum sanctum, 116-117
 symptoms of, 116
Terminalia belerica, 117

- Tulasi. *See Ocimum sanctum*
 Tulsi. *See Ocimum sanctum*
 Turmeric, 3, 10, 85, 193, 195, 196.
 See also Curcuma longa
Tylophora asthmatica. See Tylophora indica
Tylophora indica, 101-104
 Tylophorine, 101, 102
- Ukonan A-C, 17
 Ulcerative colitis, 9, 21, 33, 35, 36, 37
 United Parkinson's Disease Rating Scale, 300
 Upper Respiratory Tract Infections, 111
 plants for, 111-114
 other plants, 115-16
 Urinary stones, 151, 159
 Crataeva nurvala for, 159-160
 Urinary tract drugs, 151, 151-161
 Urinary tract infections, 151, 160
 Crataeva nurvala for, 160-161
 Ursolic acid, 10
 in *Boerhaavia diffusa*, 152
 in *Ocimum sanctum*, 93
 in *Vitex negundo*, 176
 in *Wrightia tinctoria*, 209
- Vagbhata, 2, 120, 121, 211, 302
 Vagei. *See Albizzia lebbek*
 Vajjayanti. *See Clerodendron phlomidis*
 Vairi. *See Salacia reticulata*
 Valepotriates, 303
 Valeranone. *See jatamansone*
Valeriana edulis, 303
Valeriana jatamansi. See Valeriana wallichii
Valeriana officinalis, 303
Valeriana wallichii, 303
 Vallarai. *See Centella asiatica*
 Valuluvai. *See Celastrus paniculatus*
 Vardaman pippali, 95-96
 Varun. *See Crataeva nurvala*
 Varuna. *See Crataeva nurvala*
 Vasa. *See Adhatoda vasica*
 Vasicine, 3, 87, 88
 Vasicinone, 87
 Vasodilator, 87, 123, 124
 Vatajankusa rasa, 183
- Vayasthapana drugs, 10
 Vazhai. *See Musa sapientum*
 Vedapatashala, 284
 Vedas, 2, 284
 'Vehicle' in Ayurveda. *See Ayurveda*
 Vellamata. *See Terminalia arjuna*
 Vembu. *See Azadirachta indica*
 Vendium. *See Trigonella foenum-graecum*
 Venous disorders, 146
 Centella asiatica for, 146-148
 Venous hypertension, 147, 148
 Venous insufficiency, 147, 148
 Veppalai. *See Holarrhena antidysentrica*
 Veppan. *See Azadirachta indica*
 Vesicant,
 Psoralea corylifolia, 206
 Semecarpus anacardium, 172
 Tylophora indica, 104
 Vicine, 241, 242
 Vijaysar. *See also Pterocarpus marsupium*
 Vilvam. *See Aegle marmelos*
 Viral hepatitis, 62, 64, 66, 76,
 other plants, 80-81
 Phyllanthus amarus for, 77-78,
 Viral encephalitis and *Ocimum sanctum*, 94
 Vitamin C, 10, 22, 23, 114, 220
Vitex negundo, 163
 clinical trials, 177-178
 constituents, 176
 description, 176
 external application, 168
 other names, 176
 pharmacology, 176-177
 safety, 178
 use, 176
Vitex negundo and *Commiphora mukul.*
 See Commiphora mukul
Vitex negundo and garlic and ginger,
 178
Vitex negundo var. *negundo*, 176
Vitex negundo var. *purpurescens*, 176
- Walnut, 328
 Water hyssop. *See Bacopa monnieri*
 Wedelolactone, 30, 65
 Withaferin A, 179, 289, 308

- Withania somnifera*, 163, 223
 clinical trials 180-181, 290-291, 326, 309-310, 326
 constituents, 179
 description, 179
 other names, 179
 pharmacology, 179-180, 289-290, 308-309
 safety, 181
 use, 179, 289
- Withania somnifera* and *Boerhaavia diffusa*, 309-310
- Withania somnifera*, *Cyperus rotundus* and *panchakarma*, 181
- Withania somnifera* and *Panax ginseng*, 291
- Withania somnifera* and *Smilax china*, 181
- Withania somnifera* and *Tinospora cordifolia*, 310
- Withanolides, 179, 290
 glycowithanolides, 308
- Wound healing, 194, 196, 197, 211
 and *Aloe barbadensis*, 211-214
 and *Azadirachta indica*, 218
 and *Centella asiatica*, 214-215
- Wrightia tinctoria*, 207, 208-210
- Xylocaine, 210, 333, 334
- Yashtimadhu. *See Glycyrrhiza glabra*
- Yellow-berried nightshade. *See Solanum xanthocarpum*
- Yogaraj guggul, 183
- Z- and E-guggulsterones, 132, 133
- Zingiber officinale*, 4, 5, 13-15, 163, 181-184
 clinical trials, 14-15, 39-41, 182-184
 description, 13
 other names, 13,
 pharmacology, 39, 182
 safety, 15
 traditional use, 13-14, 39, 181
- Zingiber officinale* and *Alpinia galanga*, 184
- Zingiber officinale* and *Tinospora cordifolia*, 182, 183
- Zingiber officinale*, *Vitex negundo* and *Rasna*, 182, 184