CHAPTER 1

INTRODUCTION

1.1. Herbal medicines: definition and developments.

The use of substances of plant origin for food as well as medicine can be said as old as mankind itself. Primitive man depended on plants and animals for food and medicine and learnt to identify those, which were useful to them, poisonous and harmful. As our primitive ancestors evolved in to human, the diseases they brought with them, and these acquired along the evolutionary way, became social and cultural facts as well as pathological states. Since evolution, diseases have threatened not only well being sufferers and their fellows, but also integrity of the community. Therefore it is of primary importance to the members of every group to try and maintain their health of those who fall ill.

Every human community responded to this challenge by developing a medical system. Therefore, the medical system is a "*pattern of social and cultural system that evolves to deliberate behavior to enhance health*" [1]. Ever since the most ancient times, human beings have found remedies within their habitat, and have adopted different therapeutic strategies depending both upon climatic, pedagogical, phytogeographic and faunal characteristics, as well as peculiar cultural and sociostructural typologies [2]. Traditional systems of medicines contain beliefs and practices in order to cure illness. Such acts and avoidance that constitute preventive medicines in traditional system are often quite different from those of modern medicine.

Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products that contain active ingredients, parts of plant, or other materials, or their combination. Traditional use of herbal medicines refers to the long historical use of these medicines. Their use is well established and widely acknowledged to the safe and effective, and accepted by national authorities.

World Health Organization (WHO) has defined herbal medicines as " finished labeled medicinal products that contain active ingredients, aerial or underground parts of the plant or other plant materials or combinations thereof, whether in the crude state or as plant preparations". The same WHO document adds, " medicines containing plant

material combined with chemically defined active substances, including chemically defined isolated constituents of plants are not considered to be herbal medicines".

Herbal medicines, as defined by WHO, can therefore be classified into three categories as follows:

- Phytomedicines or phytopharmaceuticals sold as over- the- counter (OTC) products in modern dosage forms such as tablets, capsules and liquids for oral use.
- Dietary supplements containing herbal products, also called nutraceuticals, available in modern dosage forms.

  Consumers in developed countries and these in urban areas of developing countries use these two types of herbal medicines. These herbal medicines are gradually occupying increasing shelf-shape in modern pharmacies.
- Herbal medicines consisting of crude, semiprocessed or processed medicinal plants. These have a vital place in primary healthcare in developing countries.

Early human recognized their dependence on nature in both health and illness. Led by instinct, taste, and experience, primitive men and women treated illness by using plants, animal parts, and minerals that were not part of their usual diet. Physical evidence of use of herbal remedies goes back some 60,000 years to a burial site of a Neanderthal man uncovered in 1960 [(3)]. In a cave in northern Iraq, scientists found what appeared to be ordinary human bones. An analysis of the soil around the bones revealed extraordinary quantities of plant pollen that could not have been introduced accidentally at the burial site. Someone in the small cave community had consciously gathered eight species of plants to surround the dead man. Seven of these are medicinal plants still used throughout the herbal world [(4)]. All cultures have long folk medicine histories that include the use of plants. Even in ancient cultures, people methodically and scientifically collected information on herbs and developed well-defined herbal Pharmacopoeias. Indeed, well into the 20th century much of the Pharmacopoeia of scientific medicine was derived from the herbal lore of native peoples. Many drugs, including strychnine, vincristine, taxol, curare, and ergot, are of herbal origin. About one-quarter of the prescription drugs dispensed by community pharmacies in the United States contain at least one active ingredient derived from plant material [(5)].

Middle East medicine. The invention of writing was a focus around which herbal knowledge could accumulate and grow. The first written records detailing the use of herbs in the treatment of illness are the Mesopotamian clay tablet writings and the Egyptian papyrus. About 2000 B.C., King Assurbanipal of Sumeria ordered the compilation of the first known materia medica--an ancient form of today's United States Pharmacopoeia containing 250 herbal drugs (including garlic, still a favorite of herbal doctors). The Ebers Papyrus, the most important of the preserved Egyptian manuscripts, was written around 1500 B.C. and includes much earlier information. It contains 876 prescriptions made up of more than 500 different substances, including many herbs [(6)].

Greece and Rome. One of the earliest materia medica was the Rhizotomikon, written by Diocles of Caryotos, a pupil of Aristotle. Unfortunately, the book is now lost. Other Greek and Roman compilations followed, but none was as important or influential as that written by Dioscorides in the 1st century A.D., better known by its Latin name De Materia Medica. This text contains 950 curative substances, of which 600 are plant products and the rest are of animal or mineral origin [(6)]. Each entry includes a drawing, a description of the plant, an account of its medicinal qualities and method of preparation, and warnings about undesirable effects.

Muslim world. The Arabs preserved and built on the body of knowledge of the Greco-Roman period as they learned of new remedies from remote places. They even introduced to the West the Chinese technique of chemically preparing minerals. The principal storehouse of the Muslim materia medica is the text of Jami of Ibn Baiar (died 1248 A.D.), which lists more than 2,000 substances, including many plant products. Eventually Christian doctors traveling with the Crusaders reintroduced this entire body of knowledge to Europe. Indeed, during the Middle Ages, trade in herbs became a vast international commerce.

China and Japan. The earliest written evidence of the medicinal use of herbs in China consists of a corpus of 11 medical works recovered from a burial site in Hunan province. The burial itself is dated 168 B.C., and the texts (written on silk) appear to have been

composed before the end of the 3rd century B.C. Some of the texts discuss exercise, diet, and channel therapy. The largest, clearest, and most important of these manuscripts, called by its discoverers Prescriptions for Fifty-Two Ailments, is predominantly a Pharmacological work. More than 250 medicinal substances are named. Most of the substances are derived from herbs and wood, grains, legumes, fruits, vegetables, and animal parts. Underlying this entire text is the view that disease is the manifestation of evil spirits, ghosts, and demons that must be repelled by incantation, rituals, and spells in addition to herbal remedies.

By the Later Han Dynasty (25-220 A.D.), medicine had changed dramatically in China. People grew more confident of their ability to observe and understand the natural world and believed that health and disease were subject to the principles of natural order. However, herbs still played an important part in successive systems of medicine. The Classic of the Materia Medica, compiled no earlier than the 1st century A.D. by unknown authors, was the first Chinese book to focus on the description of individual herbs. It includes 252 botanical substances, 45 mineral substances, and 67 animal-derived substances. For each herb there is a description of its medicinal effect, usually in terms of symptoms. Reference is made to the proper method of preparation, and toxicities are noted [4].

Since the writing of the Classic of the Materia Medica almost 2,000 years ago, the traditional Chinese Materia Medica has been steadily increasing in number. This increase has resulted from the integration into the official tradition of substances from China's folk medicine as well as from other parts of the world. Many substances now used in traditional Chinese medicine originate in places such as Southeast Asia, India, the Middle East, and the Americas. The most recent compilation of Chinese materia medica was published in 1977. The Encyclopedia of Traditional Chinese Medicine Substances (Zhong yao da ci dian), the culmination of a 25-year research project conducted by the Jiangsu College of New Medicine, contains 5,767 entries and is the most definitive compilation of China's herbal tradition to date.

Traditional Chinese medicine was brought to Japan via Korea, and Chinese-influenced Korean medicine was adapted by the Japanese during the reign of Emperor Ingyo (411-453 A.D.). Medical envoys continued to arrive from Korea throughout the next century, and by the time of the Empress Suiko (592-628 A.D.), Japanese envoys were being sent directly to China to study medicine. Towards the end of the Muromachi period (1333-1573 A.D.) the Japanese began to develop their own form of traditional oriental medicine, called kampo medicine. As traditional Chinese medicine was modified and integrated into kampo medicine, herbal medicine was markedly simplified.

In North America, early explorers traded knowledge with the Native American Indians. The tribes taught them which herbs to be used to sharpen their senses for hunting, to build endurance, and to bait their traps. In 1716, French explorer Lafitau found a species of ginseng, *Panax quinquefolius* L., growing in Iroquois territory in the New World. This American ginseng soon became an important item in world herb commerce [(7)]. The Jesuits dug up the plentiful American ginseng, sold it to the Chinese, and used the money to build schools and churches.

As medicine evolved in the United States, plants continued as a mainstay of country medicine. Approaches to plant healing passed from physician to physician, family to family. Even in America's recent past, most families used home herbal remedies to control small medical emergencies and to keep minor ailments from turning into chronic problems. During this period there was a partnership between home folk medicine and the family doctor [(8)]. Physicians often used plants and herbal preparations to treat common illness. Until the 1940s, textbooks of Pharmacognosy that characterize plants as proven-by-use prescription medicines contained hundreds of medically useful components on barks, roots, berries, leaves, resins, twigs, and flowers.

As 20th-century technology advanced and created a growing admiration for technology and technologists, simple plant-and-water remedies were gradually discarded. Today, many Americans have lost touch with their herbal heritage. Few Americans realize that many over-the-counter (OTC) and prescription drugs have their origins in medicinal

herbs. Cough drops that contain menthol, mint, horehound, or lemon are herbal preparations; chamomile and mint teas taken for digestion or stomach disorder are time-honored herbal remedies; and many simple but effective OTC ache-and pain-relieving preparations on every druggist's and grocer's shelf contain oils of camphor, menthol, or eucalyptus. Millions of Americans greet the morning with their favorite herbal stimulant--coffee.

Despite the importance of plant discoveries in the evolution of medicine, some regulatory bodies such as the U.S. Food and Drug Administration (FDA), the main U.S. regulatory agency for food and drugs consider herbal remedies to be worthless or potentially dangerous [(9)]. Indeed, today in the United States, herbal products can be marketed only as food supplements. If a manufacturer or distributor makes specific health claims about a herbal product (i.e., indicates on the label the ailment or ailments for which the product might be used) without FDA approval, the product can be pulled from store shelves.

Despite FDA's skepticism about herbal remedies, a growing number of Americans are again becoming interested in herbal preparations. This surge in interest is fueled by factors that include the following:

❖ Traditional European and North American herbs are sold in most U.S. health food stores. The same is true for Chinese and, to a lesser extent, Japanese herbal medicinals. Ayurvedic herbals are available in most large U.S. cities, as are culinary and medicinal herb shops called botanicals that sell herbs from Central and South America and Mexico. The reemergence of Native American Indian cultural influences has increased interest in Native American Indian herbal medicines.

❖ Pharmaceutical drugs are seen increasingly as over prescribed, expensive, even dangerous. Herbal remedies are seen as less expensive and less toxic.

❖ Exposure to exotic foreign foods prepared with non-European culinary herbs has led many Euroethnic Americans to examine and often consider using medicinal herbs that were brought to the United States along with ethnic culinary herbs.

❖ People increasingly are willing to "self-doctor" their medical needs by investigating and using herbs and herbal preparations. Many Americans--especially those with chronic

illnesses such as arthritis, diabetes, cancer, and AIDS are turning to herbs as adjuncts to other treatments.

India underwent a similar process in the development of its medicine. The healing that took place before India's Ayurvedic medical corpus was similar to that of ancient Egypt or China (i.e., sickness was viewed as a punishment from the gods for a particular sin). The earliest mention of the Rig Veda dates back to as early as 3500 BC. Ayurveda, considered as an Upaveda (or the supplementary Hymns designed for more detailed instruction of the mankind) has very strong foundations in the ancient medical science of India. World Health Organization estimates nearly 3200 million (80%) inhabitants of the World rely chiefly on traditional medicines for their primary healthcare needs, as a major part of traditional therapy involves the use of plant extracts or their active principles [5]. Materia medica of India provides lots of information on the folklore practices and traditional aspects of therapeutically important natural products. Indian traditional medicine is based on various systems including Ayurveda, Siddha, Unani and Yoga. It is generally believed that around one fourth of the active ingredients used in the modern medicines were derived from plant and/or plant products. Hence it will be worthwhile and beneficial to explore the plant kingdom for suitable and effective remedies and bring them into a framework of rational scientific use [10].

Ayurveda

Ayurveda is the science of life. Scattered references to health and diseases are quoted in the Vedas, especially in the Rig Veda and Atharva Veda got about 114 *hymns*, which describe the treatment of diseases, and Ayurveda has originated from those *hymns*. It is based on fundamental doctrines known as *darshanas*, which encompass physical, chemical, biological and spiritual sciences.

Ayurveda born out of intuition and revealation, developed in due course into eight well-defined specialized branches and two major schools.

- The school of physician (*Atreya sampradaya*)
- The school of surgeons (*Dhanvantari sampradaya*)

The basic theories of Ayurveda arose from the concepts of *panchamahabhutas* and *Trodosha*, which embrace the process of creation and evolution of the universe and all laws of life therein. According to Ayurveda the human body and all matter in the universe are composed of *panchamahabhutas*. Treatment of disease involves avoiding the causative factor, intake of suitable diets, adoption of appropriate activities and regimens, which would restore the balanced state of the body, or use of surgical procedures. So far as the function of the body concerned this system considers the body, mind and soul as complementary to one another. Thus Ayurveda is not merely medical science but is in fact a way of life [11].

Siddha

The Siddha system of medicine owes its origin to the Dravidian culture, which is of prevedic period. The ancient literature revealed that the Vedic Aryas owed allegiance to the cult of Shiva and worship of the phallus (*linga*), which was later, incorporated into the Vedic culture. The Shiva cult is associated with its medical counterpart, the Siddha system of medicine, which is mainly therapeutic. Mercury, sulfur, iron, copper, gold, bitumen, white, yellow and other minerals as well as vegetable poisons are extensively used in the Pharmacopoeia of the Siddha tradition. The Siddha system of medicine is prevalent in the southern states of India as well as in Sri Lanka, Malaysia and Singapore where the Dravidian civilization was dominant. The principles and doctrines of this system are both fundamental and applied and have a close similarity to Ayurveda [11].

Unani

Unani Tibb or Graeco-Arab medicine traced back to the system of Greek medicine, which was developed during Arab civilization. The basic framework of this system consists of the four humor theory of Hippocrates, which presupposes the presence of four humors; blood: phlegm, yellow bile and black bile. The basic philosophy of Tibb advocates that the body is composed of matter and spirit. These were taken, as a whole because harmonious life is possible only when there is a proper balance between bodily (physical) and spiritual (mental) function. Unani Tibb seeks the restoration of the body as a whole to its original state [12].

Yoga

Yoga is a traditional science based on techniques. It helps us to coordinate body and mind more effectively and enables a person to maintain tranquility of mind with greater calmness in the conscious state, and is perhaps the easiest and safest method to promote mental health. It can also be used as a preventive and curative technique for the management of various psychic and psychosomatic disorders. Although yoga had been described in the *Vedas* about 4000 years ago, it was presented by sage Patanjali in an abridged form about 2500 years ago [13].

His methods of integrated yoga are the most important and these are:

- *Yama* or improvement in our social behaviour
- *Niyama* or improvement in our personal behaviour
- Physical postures
- Breath holding practices
- Contemplation
- Meditation
- Attainment of super consciousness.

Regular practice of the integrated yoga can prevent the development of various psychosomatic disorders and also improve individual's resistance and ability to endure stressful situation more effectively [14,15]. Studies on normal individuals showed that a regular practice of yogic postures leads to psychological improvement in the intelligence and memory quotient and a decrease in the pulse rate, blood pressure, respiration and body weight. The integrated type of yoga has been used for the treatment of many stress disorders like hypertension, anxiety, neurosis, mucous colitis, bronchial asthma, diabetes mellitus, migraine and rheumatic disorders of the spine. In addition to the integrated practice of yoga, many other methods of yoga are available that could be used for the promotion of mental health, among them, the practice of *Kundalini* yoga [16] is the most important one.

1.2. Herbal medicines: a valuable therapy for different diseases [17, 18]

Herbal medicines remain the major source of health care for the world population. WHO has recognized herbal medicine as an essential building block for primary health care of vast countries like India and China. They are prepared from a variety of plant material like leaf, stem, root, bark and so on. They usually contain many biologically active ingredients and are used primarily for treating mild or chronic ailments. Herbs can be prepared at home in many ways, either fresh or dried ingredients. Herbal teas and infusions can be steeped to varying strengths. Roots, bark or other plant parts can be boiled into strong solutions called decoctions. Honey or sugar can be added to infusions and decoctions to make sweet. Herbal remedies can also be purchased in the form of pills, capsules or powders, or in more concentrated liquid forms called extracts and tinctures. They can be applied topically in form of creams or ointments, soaked into cloths and used as compresses, or applied directly to the skin as poultices. According to World Health Organization 80 percent of global population still depends on traditional or alternative medicine as the preferred form of healthcare, even with the spectacular advances in molecular biology, hospital medicine and physiological chemistry that have greatly enhanced our understanding and treatment of diseases.

Herb based therapies of traditional medical system is now recommended for the treatment of several degenerative and chronic diseases where modern pharmaceutical agents have proved inadequate. The acceptance of these techniques as standard healthcare options has posed serious conceptual problems in the development of public health programs that are responsible for the real needs of the population, with a tremendous impact in the cost of healthcare inventions, preventive medicine and self healing. The major characteristics of modern and traditional medicines are given in Table 1.1. Plants are considered to be medicinal if they possess pharmacological activities of possible therapeutic use. In spite of advances in modern system of medicine, there are various areas like tropical diseases, herpes, AIDS, cancer, and bronchial asthma etc., which will remain a formidable challenge to present day drug therapy. There is a possibility of finding a cure for them from the drugs of herbal origin. Almost half of the useful drugs today are derived from natural sources. Herbal medicines have yielded many useful compounds and plant

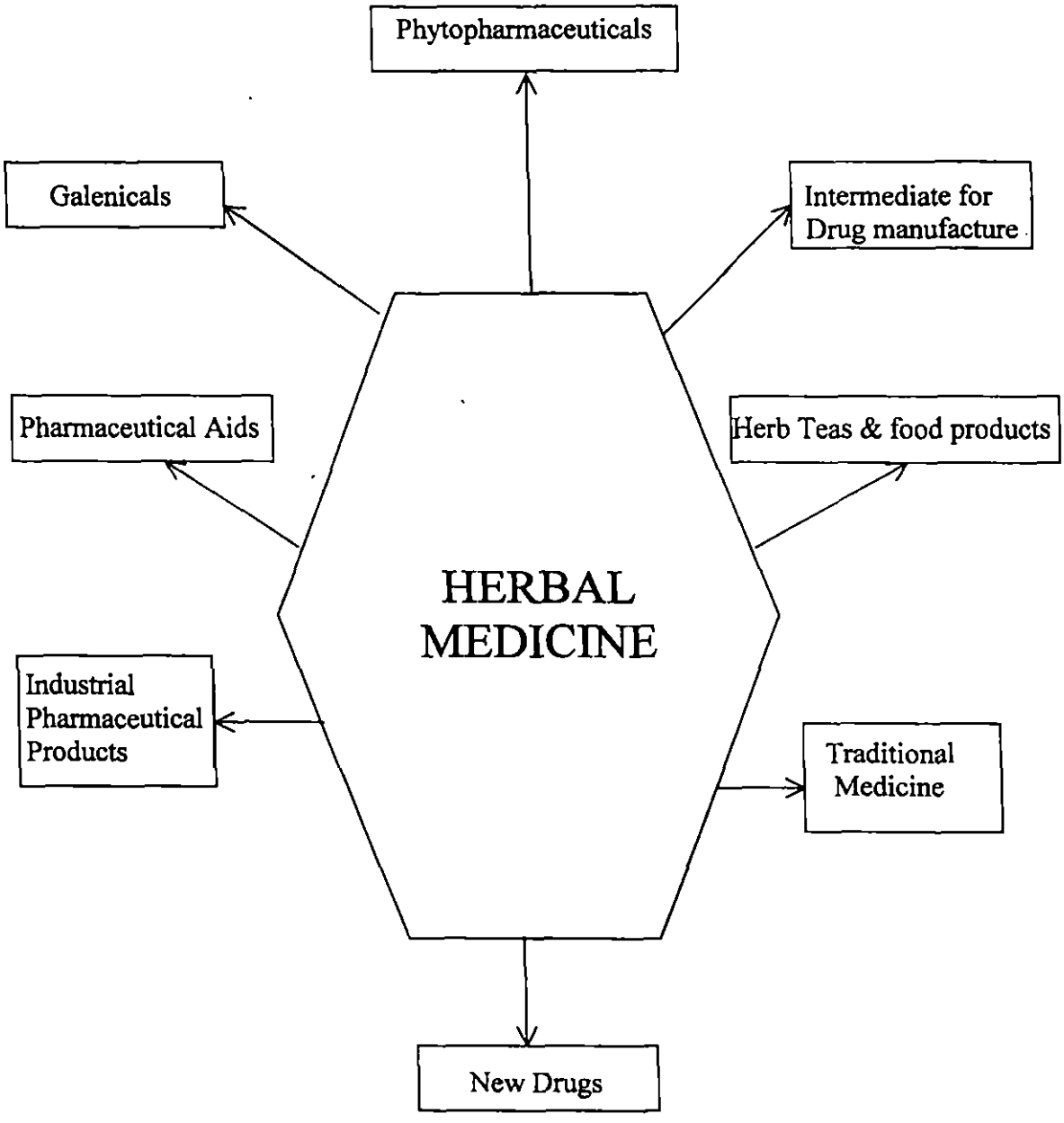

Figure 1.1 Role of Herbal Medicine.

derived ingredients, which are important components of modern phytopharmaceuticals. Today, the global market is floated with herbal preparations. A number of companies, including some multinational are entering into the area of herbal medicines. These medicines are available for each and every disorder including diabetes, ulcer, cancer, inflammation, hepatitis and asthma.

1.3. Drug discovery from natural products.

Natural products, including plants, animals and minerals have been the basis of treatment of human diseases. History of medicine dates back practically to the existence of human civilization. The current accepted modern medicine or allopathy has gradually developed over the years by scientific and observational efforts of scientists.

However, the basis of its development remains rooted in traditional medicine and therapies. The history of medicine includes many ludicrous therapies. Nevertheless, ancient wisdom has been the basis of modern medicine and will remain as important source of future medicine and therapeutics. The future of drug discovery from natural products will be more holistic, personalized and involve wide use of ancient and modern therapeutic skills in a complementary manner so that maximum benefits the patients and the community [17]. The approaches for drug development from natural sources generally consist of the steps as shown in Figure 1.2. The Greek physician Galen (AD 129–200) devised the first Pharmacopoeia describing the appearance, properties and use of many plants of his time. The foundations of the modern Pharmaceutical industry were laid when techniques were developed to produce synthetic replacements for many of the medicines that had been derived from the forest. Natural products chemistry actually began with the work of Serturner, who first isolated morphine from opium. This, in turn, was obtained from opium poppy (*Papaver somniferum*) by processes that have been used for over 5000 years. Many such similar developments followed. Quinine from cinchona tree had its origin in the royal households of the South American Incas. Before the first European explorers arrived, the native people of the America had developed complex medical systems replete with diagnosis and treatment of physical as well as mental illnesses.

Table 1.1 Salient features of modern and traditional medicines.

Modern medicine	Traditional medicine
• Universally accepted and globally spread	• Based on culture. Practice is regionalized without absolute uniformity.
• Training is intense standardized and confirmed by certification and registration	• Training varies; generally trained by a single mentor, confirmed with jewelry or dressings.
• Based on the disease	• Believes in holistic approach.
• Practice is institutionalized and developed through scientific studies	• Home serves as clinic or patients are called home for consultation and treatment
• Categorized on specialities i.e. doctor, nurse, physiotherapist etc.	• Healers may be called as specialist
• It is expensive and not easily available in remote areas	• Being culture based, healers are accessible and affordable.
• Treatment provided by doctors to physically and mentally illed patients.	• Traditional healers are highly respected, relatively old people and are vary renowned in primary health care system.

Indigenous people derived medicines and poisons from thousands of plants. A review of some plants that originated from Central and South America indicates that most of them either had potentially toxic characters or components of food sources. The following are few examples [18]: In the early 1500s, Indian fever bark was one of the first medicinal plants to find appreciative consumers in Europe. Taken from the cinchona tree (*Cinchona officinalis*), the bark was used as an infusion by native people of the Andes and Amazon highlands to treat fevers. Jesuit missionaries brought the bark back to Europe. By the early sixteenth century, this medicine was known as 'Jesuit fever bark', quite a transformation. The name coca (*Erythroxylum coca*) comes from an Aymara word meaning 'tree'. In Andean cultures, the leaves of the coca tree have been primarily chewed to obtain perceived benefits. From ancient times, indigenous people have added alkaline materials such as crushed seashells or burnt plant ashes to the leaves in order to accentuate the pharmacologically active moiety of coca. In 1860, a German chemist Carl Koler isolated cocaine, the chemical responsible for the biological activity. He found that cocaine could act as a local anesthetic in eye surgery. As the years passed, scientists observed that cocaine paralyzed nerve endings responsible for transmitting pain. As a local anesthetic, it revolutionized several surgical and dental procedures. Pot curare arrowhead poison used in East Amazon is predominately obtained from the species *Strychnos guianensis*. Tube curare in the West Amazon is from *Chrondrodendron omentosum*; curare in modern medicine is made from this species and named as tubocurarine. The jaborandi tree (*Pilocarpus jaborandi*) secretes alkaloid rich oil. Several substances are extracted from this aromatic oil, including the alkaloid pilocarpine, a weapon against the eye disease, glaucoma. American Indians on the island of Guadeloupe used pineapple (*Ananas comosos*) poultices to reduce inflammation in wounds and other skin injuries, to aid digestion and to cure stomach ache. In 1891, an enzyme that broke down proteins (bromelain) was isolated from the fresh juice of pineapple and was found to break down blood clots. Other pharmaceuticals that have their origin in botanicals include atropine, hyoscine, digoxin, colchicine and emetine. Reserpine, an anti-hypertensive alkaloid (*Rauwolfia serpentina*) became available as a result of work carried out by Ciba-Geigy in India. It is pertinent to note that most of these early discoveries are mainly based on traditional medicines; many products could act as poisons in toxic doses.

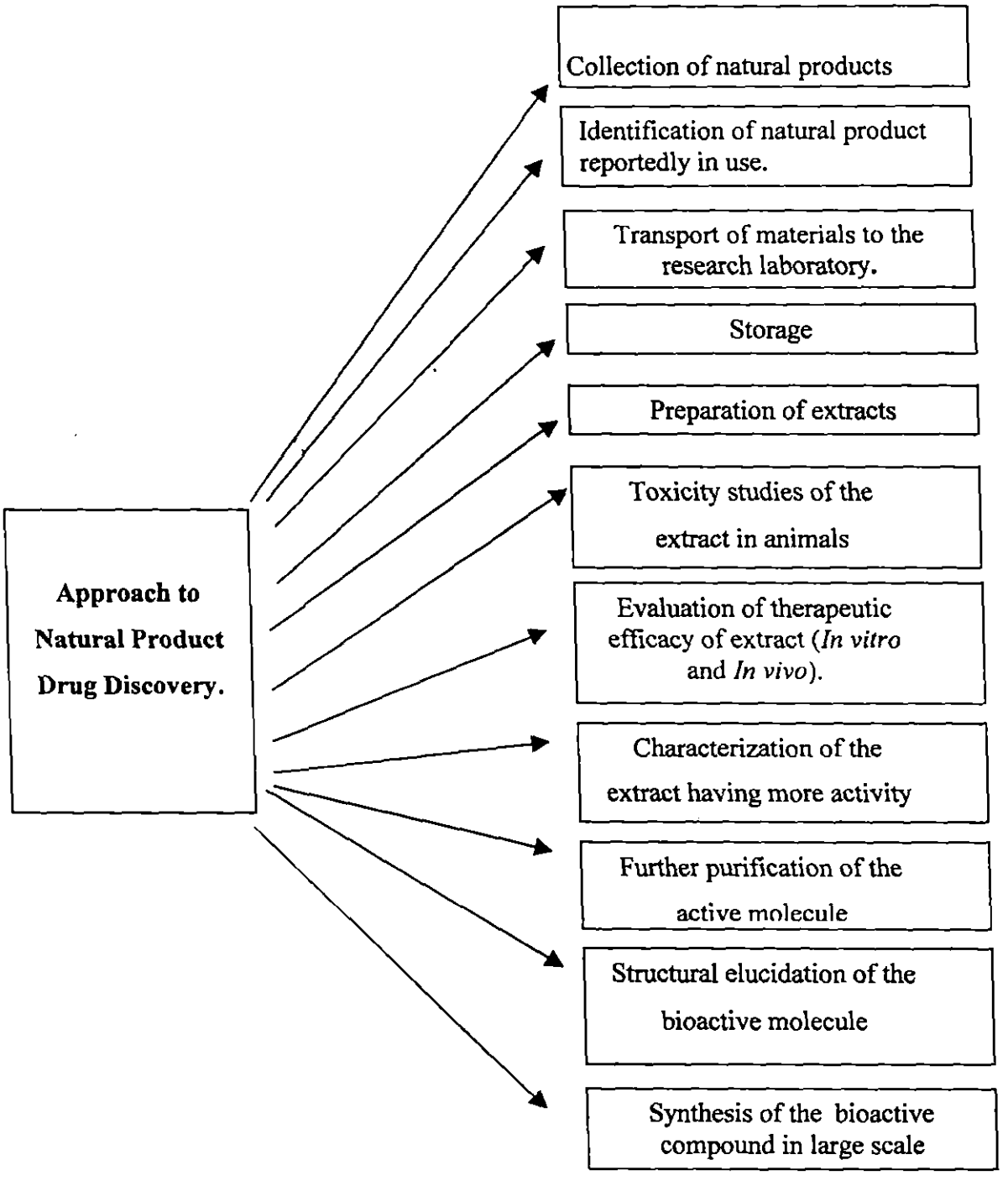

Figure 1.2. Approach for the Drug Development from Natural sources.

1.3.1. Discovering medicines or poisons?

A major problem with traditional, indigenous medicines is discovering a reliable 'living tradition' rather than relying upon second-hand accounts of their value and use. In many parts of the world the indigenous systems of medicine have almost completely broken down and disappeared. This includes mostly developed countries and some developing countries where the indigenous population has been marginalized. In others, the system is fragmented with the use of indigenous materials being limited to small tribal and geographical areas, as in many parts of Africa. In anthropological terms these are 'little traditions', while the Ayurvedic Indian and traditional Chinese systems are living 'great traditions'. Although the little traditions are an excellent repository of knowledge about medicinal and poisonous properties of botanicals, researchers have mainly exploited poisonous sources. This may be primarily because of many reasons. First, it is relatively easy to present and demonstrate poisonous characteristics of botanicals. Second, there may not be a written documentation and poisonous characters get predominance by word of mouth. Third, for an outsider, poisonous characteristics differentiate between ordinary and extraordinary material for pharmaceutical development. Fourth, a considerable time period is required to demonstrate true medicinal activities with proven safety profile. Great traditions have relatively organized database, and more exhaustive description of botanical material is available that can be tested using modern scientific methods. Ayurveda and Chinese medical systems thus have an important role in bio-prospecting of new medicines [17].

1.3.2. Serendipity and synthetic dominance

Pharmaceutical research took a major leap when alongside natural products chemistry, pharmacologists, microbiologists and biochemists began to unravel the chemistry of natural processes in human, animals, plants and microorganisms. Advances in synthetic organic chemistry led to the identification of many key chemical molecules that offered more opportunities to develop novel compounds. Many new drugs emerged by this route, particularly those now being used to treat infections, infestations, cancers, ulcers, heart and blood pressure conditions. Many drugs were developed through random screening of thousands of chemicals synthesized as dye-stuffs and the like; many others resulted from

serendipity (happy chance) arising from sharp-eyed observations of physicians and scientists. Examples of such drugs include sulfonamides, isoniazid, anti-psychotics, anti-histamines and penicillin. Emergence of the modern pharmaceutical industry is an outcome of all these different activities that developed potent single molecules with highly selective activity for a wide variety of ailments. The drugs produced in many cases improved with nature, viz. a new range of local anaesthetics from cocaine avoided its dangerous effects on blood pressure; chloroquine is much less toxic than quinine. These successes and many more like them resulted in reduced interest in natural products drug discovery and many major drug companies almost neglected such divisions. Work on developing new drugs for the treatment of the world's major diseases, malaria, trypanosomiasis, filariasis, tuberculosis, schistosomiasis, leshmaniasis and amoebiasis came almost to a standstill. In addition, although botanical medications continued to be produced in every country, the clinical efficacy of these was usually not evaluated and the composition of these complex mixtures was only crudely analysed. Thus, herbal medicines became the domain of 'old wives' tales' and quack medicine, exploitation of the sick, the desperate and the gullible. Sadly, herbal medicines continued to reflect poor quality control both for materials and clinical efficacy [17, 18].

1.3.3. Back to traditional wisdom

Lag phase for botanical medicines is now rapidly changing for a number of reasons. Problems with drug-resistant microorganisms, side effects of modern drugs, and emerging diseases where no medicines are available, have stimulated renewed interest in plants as a significant source of new medicines. Pharmaceutical scientists are experiencing difficulty in identifying new lead structures, templates and scaffolds in the finite world of chemical diversity. A number of synthetic drugs have adverse and unacceptable side effects. There have been impressive successes with botanical medicines, most notably quinghaosu, artemisinin from Chinese medicine. Considerable research on pharmacognosy, chemistry, pharmacology and clinical therapeutics has been carried out on Ayurvedic medicinal plants [19]. Numerous molecules have come out of Ayurvedic experiential base, examples include rauwolfia alkaloids for hypertension, psoralens in vitiligo, holarrhena alkaloids in amoebiasis, guggulsterons as hypolipidemic

agents, mucuna pruriens for Parkinson's disease, piperidines as bioavailability enhancers, baccosides in mental retention, picrosides in hepatic protection, phyllanthins as antivirals, curcumine in inflammation, withanolides, and many other steroidal lactones and glycosides as immunomodulators [20]. A whole range of chronic and difficult-to-treat diseases such as cancers, cardiovascular disease, diabetes, rheumatism and AIDS, all require new effective drugs. Most developing countries have relied and will continue to rely on traditional natural medicines due to the deterrence of high costs of modern allopathic medicines. Current estimates indicate that about 80% of people in developing countries still rely on traditional medicine based largely on various species of plants and animals for their primary healthcare. The uses of alternative medicine therapy in US have been increased by almost 50% from 1990 to 1997 [21].

1.3.4. Botanical medicine: research, development and markets

Thirty per cent of the worldwide sales of drugs are based on natural products. Though recombinant proteins and peptides account for increasing sales rates, the superiority of low-molecular mass compounds in human disease therapy remains undisputed mainly due to more favorable compliance and bioavailability properties. Approaches to improve and accelerate the joint drug discovery and development process are expected to take place mainly from innovation in drug target elucidation and lead structure discovery. Therefore, Grabley and Thiericke [21] have correctly emphasized the need for new concepts to generate collection of large compounds with improved structural diversity.

There are number of problems connected with the search for new prototype drugs of biological origin. Investigations of plants used in traditional and modern medicine in China serve as a source of inspiration and as models for the synthesis of new drugs with better therapeutic, chemical or physical properties than the original compounds [22]. The World Health Organization also has recognized the importance of traditional medicine and has been active in creating strategies, guidelines and standards for botanical medicines.

Commercially, these plant-derived medicines are worth about US$ 14 billion a year in the United States and US$ 40 billion worldwide. Americans paid an estimated US$ 21.2 billion for services provided by alternative medicine practitioners [23]. A 1997 survey estimated that over 12% of adults had used herbal medicine during 1996 compared with 2.5% in 1990, resulting in a increase in business of US$ 5.1 billion [24]. Lilly Research Laboratories markets several million dollars worth of vincristine and vinblastine – the periwinkle derivatives used to treat childhood leukaemia and Hodgkin's disease. The US National Cancer Institute regularly earmarks large appropriations to screen 50,000 natural substances for activity against cancer cell lines and the AIDS virus. China, Germany, India and Japan, among others, are also screening wild species for new drugs.

Proven agro-industrial technologies need to be applied to the cultivation and processing of medicinal plants and the manufacture of herbal medicines [25]. The mass screening of plants in the search for new drugs is vastly expensive and inefficient. It would be cheaper and perhaps more productive to re-examine plant remedies described in ancient and medieval texts [26]. Many higher plants produce economically important organic compounds such as oils, resins, tannins, natural rubber, gums, waxes, dyes, flavours, fragrances, pharmaceuticals and pesticides. Advances in biotechnology, particularly methods for culturing plant cells and tissues, should provide new means for the commercial processing of even rare plants and the chemicals that they produce. These new technologies will extend and enhance the usefulness of plants as renewable resources of valuable chemicals. In future, biologically active, plant-derived chemicals can be expected to play an increasingly significant role in the commercial development of new products for regulating plant growth and for insect and weed control [27].

Natural products research continues to explore a variety of lead structures, which may be used as templates for the development of new drugs by the pharmaceutical industries. While microbial products have been the mainstay of industrial natural products discovery, in recent years phytochemistry has again become a field of active interest. Drug discovery programmes based on microbial products and phytochemicals have been discussed and contrasted [28]. Glaxo PLC, embarked a programme wherein extracts and

fermentation broths were screened in order to detect bioactive principles [29]. Many other multinationals and academic institutions have created joint programmes for plant medicine research, for example, Virginia Polytechnic Institute, Bedrijf Geneesmiddelen Voorziening Suriname, Conservation International–Suriname, and Bristol–Myers Squibb Pharmaceutical Research Institute. Several such projects were sponsored by the Federal Agencies of USA. University of Chicago at Illinois, University of Mississippi, Xeenova, Ayur-Core, Inc. and Bio-Ved Pharmaceuticals represent additional examples. Indian pharmaceutical companies have launched new projects: Dabur, Zandu, Arya Vaidya, Nicholas Piramal, Lupin and Ranbaxy are few prominent examples. The Pharmaceutical Research and Development Committee (PRDC), under the Ministry of Chemicals, Government of India also underlines the importance of traditional medicines [30].

Opportunities for multidisciplinary research that joins the forces of natural products chemistry, molecular and cellular biology, synthetic and analytical chemistry, biochemistry and pharmacology to exploit the vast diversity of chemical structures and biological activities of natural products are best discussed by Clark [31].

The exploration of structural chemical databases comprising a wide variety of chemotypes, in conjunction with databases on target genes and proteins, will facilitate the creation of new chemical entities through computational molecular modeling for pharmacological evaluation [32, 33]. In natural drug discovery it is important to follow systems-theory and systems-biology applications to facilitate the processes [34]. Routine random efforts are not likely to increase the desired success rate of discovery, while experience indicates that a modified collection policy offered better chances for the discovery and development of agents for treatment of AIDS and cancer [35, 36]. Numerous drugs have entered the International Pharmacopoeia through ethnobotany and traditional medicines [37, 38]. There are many similarities in traditional systems of medicine as well as ethnomedicines being connected to each other as 'great traditions and little traditions'. All botanical drugs will have to fulfill the international requirements on quality, safety and efficacy [39].

1.3.5. Drug discovery: intentional not coincidental

In the sequence of their appearance, the scientific disciplines involved in drug discovery were chemistry, pharmacology, physiology, microbiology, biochemistry and molecular biology. It can be shown that new therapeutic classes of drugs like muscle relaxants, diuretics, antibiotics, recombinant proteins, monoclonal antibodies and others were generated on the basis of scientific opportunities rather than therapeutic need. All these drugs were created within the confines of a chemical paradigm of medicine and drug therapy. We are now witnessing the entry of a new informational paradigm into medicine that is most prominently represented by genomic sciences. This paradigm will bring two important changes in the therapy of diseases. First, molecular biology has matured to such a degree that it can now study complex genomes and their functionality in complex organisms such as humans. Therefore, results from these studies no longer have to be translated into the context of medicine: they are already within this context. Secondly, drug therapy that used to be largely symptomatic, will now aim at targets that are closer to the causes of diseases. Therapeutic progress, which used to be indirect, conjectural and coincidental, is about to become more directed, definitive and intentional. The future drug discovery will be more often based on intent rather than coincidence. Proper bioprospecting of medicinal sources will be an important factor [40].

1.4. Ethnopharmacology in drug evaluation

Interest in traditional drugs is thus not new but has been spurred in recent years by methodological advances in phytochemistry, a growing number of ethnobotanical studies, and a upsurge of interest in renewable resources in traditional medicine.

The observation, identification, description and experimental investigation of the ingredients and the effects of indigenous drugs are a truly interdisciplinary field of research. The term Ethnopharmacology has been used loosely to describe this field [44]. Ethnopharmacologic research is based on botany, pharmacology and chemistry, but other disciplines have made vital contributions. Based on these considerations, Ethnopharmacology is defined as " the interdisciplinary scientific exploration of biologically active agents traditionally employed or observed by man" [45]. This study of

traditional drugs is not meant to advocate a return to the use of these remedies in their aboriginal form, or to exploit traditional medicines. The objectives of ethnopharmacology are to rescue and document an important cultural heritage before it is lost, and to investigate and evaluate the agents employed. Thus, it plays an immense role in evaluation of natural products and more particularly the herbal drugs from traditional and folklore resources.

1.5. Phytochemical analysis of ethnomedicine

Phytochemical studies should be tailored to match the biological activity. The chemical studies should provide information that will be used in the standardization and quality control of the finished product. Even when the product is used as whole herbs, it is imperative that the chemistry of the plant material be thoroughly studied so that storage conditions, stability and ingredient integrity can be determined. For example, it will be important to determine the stability if active constituent in a crude drug is a glycoside, which will likely hydrolyze when stored with high moisture content. Isolation of phytoconstituents using Coloumn chromatography monitor by Thin layer chromatography and finally confirmation of structure by using various spectral methods like IR spectroscopy, ^{1}HNMR Spectroscopy, ^{13}CNMR Spectroscopy and Mass Spectroscopy are involved in phytochemical investigation [41].

1.6. Toxicity studies of ethnomedicine

Herbal products used in traditional medicines are generally non-toxic due to dilution with inert herbal ingredients. The traditional system of medicines advocates a liquid dosage form, which encourages the use of extremely low concentration of active ingredients in the finished products. The problem of toxicity of synthetic drugs arises mainly due to modification of the original structure to increase the biological activity. In the traditional formulations, therapeutically active substances in plants exist in conjunction, and bound with other substances like tannins, carbohydrates, amino acids, proteins, vitamins, trace metals, etc. and consumed as decoctions. Moreover major part of the formulations remain as food materials and consumed by the human body along with the therapeutically active substances. When used in the right form, these herbs do not upset or cause toxicity in the

body, rather they maintain the physiological balance of the body. This explains why herbal extracts produce little or no toxicity, even when large amount is consumed. Over processing food is not beneficial in promotion of condition of health.

Among so many co-existed compounds in the plants one may exist in the state of highly reactive. It has been suggested that the reactivity of the single compound with the physiological mediators of the human systems leads to the manifestation of the phenomenon described as drug toxicity. Phytomedicines, with a little amount of processing, can be considered as health foods. They promote the health since they contain, apart from the active drug molecule, other substances required to maintain the overall physiological functions of the body. This is why "bitter leaf" (*Vernonia amygdalina*) can be used as a food and as a drug in the treatment of diabetes, without any manifestation of toxicity. However, when purified extracts or isolated compounds are used as phytomedicines, they should be subjected to same rigorous testing procedures used to standardize other medicinal agents.

1.7. Pharmacological evaluation of ethnomedicine

The single major factor, on which the decision to select one or more medicinal plant candidates for development into phytomedicines on commercial scale is the wealth of ethnomedicinal information on its efficacious use in the long history of traditional medicines. The scientific literature is now replete with reproducible experimental results on the pharmacological properties of herbal extracts. These results were obtained using the same laboratory animal models and techniques that have been accepted scientifically for testing the pharmacological activity of the pharmaceutical products [42,43]. Modern chemical methods have led to a dramatic increase in the number of natural or synthetic molecules available for pharmaceutical research. At the same time, recent developments in cellular and molecular pharmacology provide an increasing number of selective tests able to identify the activity and the mechanisms of action of biologically active molecules. Paradoxically, however, the availability of numerous sophisticated techniques makes the pharmacological research much easier. A major problem encountered in the pharmacological evaluation of plant drugs is that of solubility. The active constituents

occur naturally as soluble salts or organic complexes with solubility enhancing matrices, but the extraction process sometimes leads to the dissociation of the organic compounds from the water-soluble components with the resultant production of insoluble extractives. Problem arises from attempts to resolubilize the material in aqueous media for pharmacological evaluation, and the use of organic solvents is often precluded because of probable interference with bioassay methods.

1.8. Clinical evaluation of ethnomedicine

Prior to detailed laboratory studies of any plant used in traditional medicine, it is important to establish whether the remedy does in fact posses the claimed therapeutic properties. It is important to emphasize the fact that a given plant may not show pharmacological activity in laboratory animals but it does not necessarily mean that the plant devoid of therapeutic application. A carefully designed clinical evaluation will help to determine if the remedy is active within measurable parameters. Such studies are not the same with a clinical trial of a new drug entity. This form of evaluation merely evaluates the traditional use of the drug in a clinical setting. The usual ethical considerations are followed, and the dosage form is standardized in terms of posology. It is not supposed to address any of the issues meant for a controlled clinical study. It is neither randomized nor double blinded. Good reliable results can obtain for most diseases with a small study population of 8 to12. It should, however, provide clear go/no go decision points [45]. Conducting a clinical evaluation at the beginning of the study will give the candidate drugs a better chance of making it as a reliable indicator of substances that can be used in the production of effective and safe phytomedicines and natural personal care products.

Perhaps clinical evaluation of traditional medicine is even more useful not as a tool for pharmaceutical drug discovery but as a method to provide a better understanding of the spectrum of activity or limitations of ethnomedical remedies and practices. In this case establishment of clear and unambiguous parameters for measuring expected outcomes is required. Three fundamental features determine the scientific rigor and validity of the experimental approach to assessing herbal efficacy: Randomization is the hallmark of the randomized controlled trial (RCT), ensures that the various treatment groups are indeed

comparable and that the only significant difference is the treatment they receive. Blindness minimizes bias by both patient and investigator, and could be considered crucial in a system of medicine that is relatively more subjective than modern medicine. The third leg of the RCT tripod is the measurement of predetermined outcomes that should complete, appropriate, and accurate. As has been noted by Keravitz, measurement of predetermined outcomes is a property that is recommended not only for RCT but also for good observational studies used in the evaluation of herbal medicines. The overriding consideration in determining the outcomes should be the interest of the patient, since ultimately the objective is to improve their health status. Both generic and disease specific outcomes are now combined in the determination of the usefulness of therapeutic interventions in complex clinical situations. In certain situations, measurement of various aspects of functional status and well-being and other quality of life assessments are considered more relevant to the patient than disease-specific outcome measurements [46]. It has been observed that although RCT is a valuable method for the evaluation of ethnomedical remedies and the so-called complementary and alternative medicines, the method may have some important drawbacks that could limit its application in ethnomedical evaluation [47].

Some of the problems with the RCT method include generalizability of the results produced because the study populations are often limited to a fairly narrow spectrum of patients that may not be representative of either the population or the situation in actual practice in order to enhance internal validity and to keep sample sizes reasonable [47]. The results obtained from RCT's are also rendered less relevant to real life situations by the mere fact that the experiments are usually conducted by experienced clinical investigators, and the careful monitoring of the patients in a clinical trial setting may produce results that are better than real situations. In order to overcome the limitation of the RCT approach for clinical evaluation of ethnomedical remedies, alternative approaches have been suggested that attempt to narrow the difference between efficacy and effectiveness.

These alternative approaches include:

- *Quasi-experimentals*: Patients are assigned to treatment condition not as individuals but as members of a group. This method dispenses with randomization and blindness but solves the problem of selection bias that is common with evaluation of traditional medicines.

- *Regression-discontinuity*: The designed is not randomized but provides for full experimental control without randomization. It is based on the assumption that there are predictable relationships between pre-test and post-test scores for all subjects. By using the same patients as controls, it is possible to determine the effect of a given therapy by assessing the observed difference between the regression linear obtained by plotting the pre-test scores and the post treatment effects.

- *Cohort studies*: This involves following a group of patients in time. Both prospective (forward in time) and retrospective cohort studies are valid approaches to assess the effect of a given therapy.

- *N=1 trials*: These are conducted with just one individual patient, with all the rigor and a true experimental approach. The experiment can be blinded, and definitive decisions can be made regarding the efficacy of a given treatment on the individual patient.

- *Case control studies*: patients are selected based on the presence or absence of the diseases or outcome of interest t time t=0. Assessment is then made on the exposure status of both cases at an earlier time (t=1). This time is particularly useful in epidemiological research.

1.9. New drug molecules from nature

Throughout the ages humans are relied on nature for their basic needs, be it for food, shelter or medicine. Plants formed the basis of sophisticated traditional system that has been in existence for thousands of years in countries such as India and China.

The use of plants in the traditional medicinal system of many other cultures has been extensively documented. These plant-based systems continue to play an essential role in health care, and as discussed earlier, it has been estimated by the World Health Organization that approximately 80 percent of the world's inhabitants rely mainly on traditional medicines for the primary health care. Plant products also play an important role in the healthcare systems of the remaining 20 percent of the population, mainly residing in the developed countries. Table 2 represents the model lists of medicinal plants that were recommended by WHO for different therapeutic activity.

Today, pharmaceutical companies have to spend millions of dollars to develop a new drug molecule. Currently, approaches to improve and accelerate the joint drug discovery and development process are expected to arise mainly from innovation in drug target elucidation and lead finding. Therefore, new concepts to generate compound libraries with improved structural diversity are desirable and it can be provided by natural products due to wide chemical diversity. It is necessary to discover and develop new drugs in such a way as to maximize the return on the investment. Natural products can stand as a good alternative in finding drug molecules at low cost and in time frame with newer developments in the field.

A recent survey has found that 477 out of 868 drug molecules discovered from various sources during the period of 1981 to 2002 were natural products or derived from the natural products i.e. almost 55 percent of the drugs discovered till date [48]. In 2000 alone, seven out of twenty best-selling non-protein drugs were either derived from natural products, or developed as a result of lead compounds generated from natural product sources. These included several statins, the largest selling class of drugs, enalaprils and augmentin, with combined annual sales in excess of US $ 20 billion. Although natural products constitute only one percent of all published chemical structures, yet natural products and substances derived naturally account for about 35 percent of the total pharmaceutical market. The key advantage of natural products over synthetic compounds is their greater chemical diversity. Although, it has been estimated that less than 10 percent of biodiversity has been tested for biological activity, a comparison of the

structure of compounds in published data base revealed that 40 percent of the chemical scaffolds found in natural products are absent in synthetic chemistry.

A number of natural products and natural product-derived compounds are in the market as drug molecules in various therapeutic categories [48]. The recent examples are Ertapenam (Antibacterial, 2002), Micafungin (Antifungal, 2002), Abacavir (Antiviral, 1999), Frovatriptan (Antimigraine, 2002), Zofenapril (Antihypertensive, 2000), Arglabin (Anticancer, 1999), Gefitinib (Anticancer, 2002) and many more. So, there is an urgent need to identify novel, active chemotypes as lead compounds for effective drug development in many therapeutic areas. Drug discovery from nature was de-emphasised at a time when there has been rapid progress in technology that could have enhanced the process of drug discovery. There is a need to re-emphasise and enhance research in natural products, because only a small fraction of plant species has been investigated so far.

1.10. Scope and aim of phytomedicine in the near future

The scope and aim of the phytomedicine in near future will be its extensive research, regardless of whether phytopharmaceuticals are classified as conventional or traditional drugs. As we enter into a new millennium, it may be urged that interest in herbal medicines and natural products in general is at an all-time high. The last decade has witnessed a greater use of botanical products among members of the general public through self-medication than never before. This phenomenon has been mirrored by an increasing attention to phytomedicines as form of alterative therapy by the health professions inclusive of pharmacy and medicine. The search for new pharmacologically active compounds for drug development is an important issue but not the only one, as the trend toward using standardized plant extracts of high quality, safety, and efficacy will continue. Therefore, all efforts have to be targeted to reveal the chemical-pharmacological profiles of extracts and fixed combinations and to rationalize their therapeutic applications. Whether in the future the highly active, safe, and causally acting phyto-preparations will be able to replace some synthetic drugs, or in other cases are potent enough to be applied in combination with synthetic drugs, depends on the level of

evidence-based therapeutic efficacy achieved. In this context, it will also be necessary to find scientific explanations and rationales for the fact that many phyto-preparations, usually applied in low doses relative to the amount of defined bioactive compounds contained in an extract preparation, exhibit no immediate pharmacological or therapeutic effect and achieve their optimal efficacy only after long-term (three to four weeks) treatment. The greatest challenge for phytomedicine research, however, will be the shift of paradigms, which is occurring in chemotherapy. This change can be described as a withdrawal from monosubstance therapy and a transition to treatment of patients with drug combinations consisting of two, three, or more single drugs. This multi-chemotherapy has been introduced, for example, in the treatment of AIDS, hypertension, and many other diseases. The second paradigm shift can be defined as a change in the strategy of medication, characterizable as a multitarget therapy. Taking tumor therapy as an example, this new strategy aims to destroy tumor cells not via direct interaction of the drug with the tumor cell cycle but via various other mechanisms, which do not damage healthy cells. This medication could be directed, e.g., to induce apoptosis of tumor cells, to inhibit angiogenesis, to stimulate specific and nonspecific immune defense mechanisms, to induce the expression of antioncogenes, and to activate the production of cell-protecting proteins (heat shock proteins). This new, very ambitious therapeutic strategy is still in its infancy, but it is a challenge for phytomedicine research because the attempt to treat diseases according to this strategy is an actually old phytotherapeutic concept.

Table 1.2. Model list of medicinal plants recommended by WHO

Gastro intestinal tract remedies

Anti-diarrheals

Acacia arabica
Acacia catechu
Berberis aristata
Commiphora mukul
Punica granatum

Laxatives

Aloe ferox
Cassia acutifolia
Chicorium intybus
Glycyrrhiza glabra
Plantago ovata, P.psyllium
Rhamnus frangula
Ricinus communis

Carminatives

Cinnamomum zeylanicum
Elettaria cardamomum
Matricaria chamomilla
Origauni spp.
Tyhmus vulgare, Ocimum sanctum,
Umbelliferous fruits. *Pimpinella anisum*
Zingiber officinalis

Spasmolytics

Atropa belladona
Datura spp.
Hyoscyamus spp.
Solenostemma spp.

Stomachics

Rheum officinalis

Anti-emetics

Atropa belladona
Hyoscyamus spp.
Mentha spp.
Zingiber officinalis
Santalum album

Anti-helmintics

Alziba anthelmintics
Artemesia cina

Analgesics and anti-inflammatory agents

Lactuca sativa
Matricaria chamomilla
Peganun harmala

Remedies for arthritic condition

Capsicum minimum, C.annum
Commifora mukul
Withania somnifera

Remedies for eye disease

Berberis aristata
Rosa damascena

Treatment for snakebites and scorpion and insect stings

Aloe spp.
Azadirachta indica
Heliotropium strigosum

Anti-allergics

Cydonia oblonga

Remedies for upper respiratory diseases

Adhatoda vasica
Allium cepa
Althaea officinalis
Ammi visnaga
Cassia fistula
Hibiscus subdarriffa
Linum usitatissimum
Mentha spp.
Nigella sativum
Ocimum sanctum
Prunus domestica
Psidium guajuava
Tilla sometosa, T.ulmifolia

Plants reported to induce aphrodisiac effect

Aleurites moluccana
Costus speciosus
Celba pentandra
Artocarbus heterophyllus
Piper betle
Pandanus amarylifolius
Lamulus symphomonia
Areca catechu
Erythroxylum coca
Magnolifa fuscata
Ipomeoea mauritania
Semecarpus anacardium
Asparagus racemosus
Mucuna prurita
Boerhaavia diffusa
Maranta arundinacea
Canna edulis
Butea superba
Dioscorea triphylla
Piper longum

Remedies for skin diseases

Aloe vera, A. barbadenses, A. ferox
Ammi majus
Azadirachta indica
Ficus carica
Fumaria officinalis, Lasoria alba
Lupinus termis
Martricaria chamomilla
Nymphaea alba
Urginea maritima
Zingiber officinalis

Remedies for urinary infection

Ammi visnaga
Balanites aegyptiaca
Cucumis sativus
Cymbopogon prodmus
Nymphaea alba
Raphanus sativus

Treatment for burn, scals, wounds, abscesses and swellings

Aloe vera, A.barbadense, A. ferox
Lawsonia alba
Linum usitatissimum

References:

1. Dunn, F.L. (1976). Traditional Asian medicine and cosmopolitan medicine as adaptive systems. 1st ed, Berkeley, University of California Press, pp. 135-138.
2. Nichter, M. (1992). Anthropological Approaches to the study of Ethnomedicine. Amsterdam, Gordon & Breach, pp. 234-235.
3. Solecki, R.S. and Shanidar I.V. (1975). A Neanderthal flower burial of northern Iraq. *Sci* 190, 880-887.
4. Bensky, D. and A. Gamble. (1993). Chinese Herbal Medicine: Materia Medica (revised edition). Eastland Press Inc., Seattle, pp.126.
5. Farnsworth, N.R., Akerele O., Bingel A.S., Soejarta D.D. and Eno Z. (1985). Medicinal plants in therapy. *Bull World Health Organ* 63 (6), 965-981.
6. Ackerknecht, E.H. (1973). Therapeutics: from the Primitives to the Twentieth Century. Hafner Press, New York, pp. 16.
7. Duke, J.A. (1989). Ginseng: A Concise Handbook. Reference Publications Inc., Algonac, Mich, pp. 39.
8. Buchman, D.D. (1980). Herbal Medicine. Gramercy Publishing Company, New York, pp. 49.
9. Snider, S. (1991). Beware the unknown brew: herbal teas and toxicity. FDA Consumer (May), 31-33.
10. Farnsworth, N.R. (1984). How can well be dry when it is filled with water. *Econ Bot* 38, 4-13.
11. Kurup, P.N.V. (1983). Traditional medicine and health care coverage. World Health Organization, Geneva, pp. 50-58.
12. Said, H.M. (1983). Traditional medicine and health care coverage. World Health Organization Geneva, pp. 61-67.
13. Sachinanda, S. (1978). Integral yoga: the yoga sutras of Pantajali. Pomferet, CT, USA, Integral Yoga Publications.
14. Udupa, K.N. (1989). Disorders of stress and their management by yoga. *The Hindu* April 4, 3-4.

15. Udupa, K.N. and Singh, R.H. (1979). Yoga in relation to the brain pituitary adrenocortical axis in interaction with the brain pituitary adrenocortical system. London, Academic Press, pp.273.
16. Gopikrishna. (1978). *Kundalini-* The biological basis of religion and genius. Kundalini research and Publication Trust, New Delhi, pp. 24-76.
17. Patwardhan, B. and Hooper, M. (1992). Ayurveda and future drug development. *Int J Alternative Complement. Med* 10, 9-11.
18. Steven King. (1992). Medicines that changed the world. *Pac Discovery* 45, 23-31.
19. Dahanukar, S. A., Kulkarni, R. A. and Rege, N. N. (2000). Pharmacology of medicinal plants and natural products. *Ind J Pharmacol* 32, 81-118.
20. Patwardhan, B. (2000). Ayurveda: The designer medicine. *Ind Drugs* 37, 213-227.
21. Grabley, S. and Thiericke, R. (1999). Bioactive agents from natural sources: trends in discovery and application. *Adv Biochem. Eng Biotechnol* 64, 101-154.
22. Baerheim Svendsen, A. and Scheffer, J. J. (1982). Natural products in therapy. Prospects, goals and means in modern research. *Pharm Wkly.* [*Sci.*] 4, 93-103.
23. Eisenberg, D. M. (1998). Trends in alternative medicine use in US. *J Am Med Assoc* 3, 25-28.
24. De Smet. (2002). Herbal remedies. *New Engl J Med* 347, 2046-2056.
25. Akerele, O. (1993). Nature's Medicinal Bounty: Don't throw it Away. World Health Forum, WHO, Geneva, Vol. 14, pp. 390-395.
26. Holland, B. K. (1995). Prospecting for drugs in ancient texts. *Nature* 376, 546-552.
27. Balandrin, M. F., Klocke, J. A., Wurtele, E. S. and Bollinger, W. H. (1985). Natural plant chemicals: sources of industrial and medicinal materials. *Sci.* 228, 1154-1160.
28. Borris, J. (1996). Natural products research: perspectives from a major pharmaceutical company, Merck Research Laboratories. *J Ethnopharmacol* 51, 29-34.
29. Turner, D. J. (1996). Natural product source material use in the pharmaceutical industry: the Glaxo experience. *J Ethnopharmacol.* 51, 39-43.
30. Mashelkar, R. A. (1999). Transforming India into the knowledge power. PDRC Report, Government of India, November.

31. Clark, A. M. (1996). Natural products as a resource for new drugs. *Pharm Res* 13, 1133-1144.

32. Nisbet, L. J., Moore, M. and Soejarto, D. D. (1997). Will natural products remain an important source of drug research for the future? *Curr Opin Biotechnol* 8, 708-712.

33. Soejarto, D. D. (1996). Biodiversity prospecting and benefit-sharing: perspectives from the field. *J Ethnopharmacol* 51, 1-15.

34. Leroy Hood. (2003). Principles, practice and future of systems biology. *Drug Discovery Today* 8, 436-438.

35. Cragg, G. M., Boyd, M. R., Cardellina, J. H. II, Newman, D. J., Snader, K. M. and McCloud. (1994). Ethnobotany and drug discovery: the experience of the US National Cancer Institute developmental therapeutics Program, National Cancer Institute, Bethesda. *Ciba Found Symp* 185, 178-190; 190-196.

36. Kitagawa, I. (1992). Elucidation of scientific basis for traditional medicines and exploitation of new naturally occurring drugs. *Yakugaku Zasshi* 112, 1- 41.

37. De Smet, P. A. (1997). The role of plant-derived drugs and herbal medicines in healthcare. *Drugs* 54, 801-840.

38. King, S. R. and Tempesta, M. S. (1994). From shaman to human clinical trials: the role of industry in ethnobotany, conservation and community reciprocity. *Ciba Found Symp* 185, 197-206.

39. Vogel, H. G. (1991). Similarities between various systems of traditional medicine: Considerations for the future of Ethnopharmacology. *J Ethnopharmacol* 35, 179-190.

40. Drews, J. (1995). Intent and coincidence in pharmaceutical discovery. The impact of biotechnology. *Arzneim.-Forsch* 45, 934- 939.

41. Trease G.E and Evans, W.C. (1996). Pharmacognosy, 12th Edn. (ELBS publication, Baillier Tindal, East Bourne), pp. 344, 539.

42. Hostetmann, K. editor. (1991). Assay of bioactivity, Methods in plant biochemistry. Vol. 6, London: Academic press, pp. 360.

43. Bohlin, L. and Bruhn, J.G. (1999). Bioassay methods in natural product research and drug development, *Proceeding of the Phytochemical Society of Europe.* Dordrecht: Kluwer Academic, pp. 201.

44. Efron, D.H., Holmstedt B. and Kline N.S. (1967). *Ethnopharmacologic Research for Psychoactive Drugs,* Public health service Pub. No. 1645, Washington Dc, US Government Printing office.

45. Halliday, R.G., Drasdo, A.L., Lumely, C.E. and Walker, S.R. (1992). *Pharmacist Med* 6, 281-296.

46. Stewart, A and Ware, J.E. (1992). Measuring functioning and well being the medical outcomes study approach. Kutham, Duke University Press, pp. 321.

47. Kravitz, R. (1999). Evaluation of Herbal Medicines: Alternatives Randomized controlled Trial. In: Eskinazi, D., Blumenthal, M., Farnsworth, N. and Rigginis, C.W. (ed). Mary Ann Liebert, Inc, Larchmont NY, USA, pp. 123.

48. Singh, I.P., Bodiwala, S.H. (2005). New drug molecules from nature. *Exp Pharm Pulse*, February 3, 6-7.