Herbal Drugs: Ethnomedicine to Modern Medicine

K.G. Ramawat (Ed.)

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About the editor

Professor K.G. Ramawat (born in 1952) received his M.Sc. (1974) and Ph.D. (1978, Plant Biotechnology) from the University of Jodhpur, Jodhpur, India and became a faculty member in January of 1979. He joined M.L. Sukhadia University as an Associate Professor in 1991 and became a Professor in 2001. He served as Head of the Department of Botany (2001–2004), was in charge of the Department of Biotechnology (2003–2004), was a member of the task force on medicinal and aromatic plants at the Department of Biotechnology (Government of India, New Delhi; 2002–2005), and was a coordinator of the UGC-DRS and DST-FIST programs (2002–2007). He did his postdoctoral study at the University of Tours, France (1983–85) and subsequently worked as visiting professor at the University of Tours (1991) and University of Bordeaux 2, France (1995, 1999, 2003, 2006). He visited Poland under the auspices of an INSA-PAN academic exchange program (2005). He has published more than 100 research papers and review articles in reputed journals and books. He has edited two books on the biotechnology of secondary metabolites and of medicinal plants (Scientific Publishers, Enfield, USA and Springer verlag, Heidelberg, Germany). Professor Ramawat has completed several major research projects from UGC, CSIR, ICAR, DBT, and DST, and has supervised the doctoral theses of 16 students. He has been a member of the Plant Tissue Culture Association of India since 1991.

Preface

Considerable progress has been made in our healthcare system, in particular with respect to sensitive diagnostic tools, reagents and very effective and precise drugs. On the other hand, high-throughput screening technology can screen vast numbers of compounds against an array of targets in a very short time, and leads thus obtained can be further explored. In developing countries, the exploding population exerts pressure not only on natural resources but also on the human population itself, whose members strive to become successful and advance in society. This leads to increased blood pressure, anxiety, obesity-associated lipid disorders, cardiovascular diseases and diabetes. Most of these diseases result in disturbed family life, including sexual behaviour.

Despite technological developments, herbal drugs still occupy a preferential place in a majority of the population in the Third World and terminal patients in the West. Herbal drugs, in addition to being cost effective and easily accessible, have been used since time immemorial and have passed the test of time without having any side effects. The multitarget effects of herbs (holistic approaches) are the fundamental basis of their utilization. This approach is already used in traditional systems of medicine like Ayurveda, which has become more popular in the West in recent years. However, the integration of modern science with traditional uses of herbal drugs is of the utmost importance if ones wishes to use ancient knowledge for the betterment of humanity. This book will try to bridge this gap and will be a valuable source for herbalists, traditional and modern medical practitioners, and researchers in botany, ethnobotany, pharmacy, phytochemistry and agriculture. Contributions on herbs used for beneficial effects on memory, sexual behaviour, neurodegeneration, erectile dysfunction, inflammation, cardiovascular diseases, cancer prevention, stroke and central nervous system disorders will provide vital information to readers.

Finally, I would like to acknowledge my contributors, who have gone to great lengths to ensure the high scientific quality of the book. I would also like to thank my colleagues at Springer.

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Chapter 1
Medicinal Plants: A Renewable Resource for Novel Leads and Drugs

R. Verpoorte

Abstract Present-day drug development is strongly focused on finding active compounds on well-defined targets using high throughput screening approaches. Unfortunately it seems that this approach is becoming less and less successful, as in most cases already good compounds are on the market, and the rapidly rising costs of drug development will make it increasingly difficult to make an economically competitive novel drug for any major disease. In other words, the reductionist approach presently used is becoming less successful. The time has come to rethink drug development. Many Western medicines are based on traditional knowledge from Europe and the Mediteranean region. This is why interest is rapidly increasing in Indian and Chinese medicine, both of which represent a very long tradition of apparently safe use. However, these healthcare systems are different from Western medicine, so novel methods are required to verify the efficacy and safety of the therapies. As it often concerns personalized medication with complex mixtures, a reductionist approach of screening for a single active compound on a known target will in many cases not be successful, as more than one target may be involved; in addition, and complicating the situation even more, synergism and prodrugs may be involved. Systems biology as a novel holistic way of dealing with biological problems seems here an interesting option. Systems biology means proceeding without a hypothesis, just observing, measuring as many parameters as possible in a biological system and afterwards using chemometrics to reveal any meaning in the data. This approach has already proven successful in studying medicinal plants and, in combination with the classical natural-product-based drug lead finding, is expected to be a major issue in the coming years. As present-day patent laws require innovative and unexpected findings, the development of old knowledge does not fit this requirement. Therefore, to support the development of evidence-based traditional medicines, it would be of great interest if some sort of protection could be obtained for companies developing such medicines so that they could earn back their huge R&D investments.

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Keywords Herbal medicines · Traditional medicine · Systems biology

1.1 Introduction

Since ancient times humans have explored their environment for plants that could be used to cover all their basic needs: food, shelter, fuel and health. This has resulted in the use of a large number of plants; in particular, food plants' extensive breeding has resulted in high-yield crops. In the case of medicinal plants, such breeding has largely not yet taken place as nature could provide a sufficient supply. The number of medicinal plants has been estimated to be on the order of 40,000 to 70,000 [1], which means that almost 25% of all plant species have some sort of medicinal use somewhere in the world. This heritage from our ancestors has continued to develop in Western medicine and has resulted in the isolation and production of pure active compounds (e.g. morphine, atropine and digoxin) and later in the development of novel synthetic compounds based on this knowledge (e.g. local anaesthetics based on cocaine, analgesics based on morphine). Some of these synthetics based on natural products have been very successful, e.g. acetylsalicylate, which development was based on the use of Salix bark as analgesic. In other cases the result has not been so successful, e.g. the acetyl derivative of morphine (heroin). This illustrates that many medicines in the West have originated in phytotherapy, as occurred in European/Mediterranean region.

In addition, the statistics on novel drugs developed in recent decades show that natural products are a major source of inspiration for drug development [2], with only 30% of all novel molecules (of the 1184 so-called novel chemical entities or NCEs) introduced into the market in the period 1981–2006 being pure synthetic and all others being natural products or natural product related. These statistics also show that the number of novel chemical compounds reaching the market is decreasing every year. The high costs (approx. 1000 million euros) and long duration (more than 10 years), as well as the fact that for most major ailments good medicines that are already available hampers the development of novel drugs by the pharmaceutical industry. Recently problems with serious side effects caused that several novel medicines had to be taken of the market shortly after their introduction. This does not also help to increase efforts at novel drug development.

At the same time the strong emerging economies of countries like India and China have led to greater interest in local healthcare systems, which are even considered an important (cheap) alternative to expensive treatments using Western drugs (see Chapters written by Pandey et al., Melzer and Saller, and McGregor (this volume)). Moreover, after thousands of years of extensive and widespread use of traditional medicines, the question arises as to why we should not consider these medicines again using all the tools of modern science [3, 4]. Further studies may lead to the discovery of novel modes of action, novel biologically active compounds, confirmation of traditional use, or, in the worst case, the fact that no activity is present and even that a given medicine's use can carry risks of toxicity (see Chap-

ters written by Cuzzolin and Benoni, and Benoni and Cuzzolin (this volume)). With 80% of the world's population using such traditional medicine, it makes sense to devote much more resources to such studies. The discovery of the antimalarial compound artemisinin in traditional Chinese medicine some 30 years ago has led to an efficient novel medicine used to treat malaria. But it has also led to totally new potential applications, e.g. in treating cancer (see Chapter written by Efferth (this volume)). Many more hidden gems may be found through studies of traditional medicine (Please specify the title and author you are referring to.).

One of the problems in studying traditional medicines is the totally different healthcare systems they are embedded in, e.g. different ways of classifying diseases, personalized medicines, and the complex mixtures of ingredients in traditional medicines. Current approaches to drug development may pick up some interesting compounds with high activity, but high throughput screening (HTS) will only detect compounds with strong affinity to a target enzyme or receptor; it will miss prodrugs (such as salicin the compound in Salix bark that in the human body is converted via glucolysis and oxidation into salicylate). Also, the synergy between compounds will not be observed in HTS, as one may, for example, envisage that artemisinin may have synergy with other antitumor compounds in a plant. The study by Stermitz et al. [5] showing the synergy between berberine and 5′-methoxyhydnocarpin is now a classical example of synergy between two compounds from one plant. The way traditional Chinese medicines are made and the different roles that each plant traditionally was thought to play in fact point to the possible importance of synergy between ingredients [6]. A recent study on the effects of ginkgo on peripheral blood flow is a beautiful example of the totally different concept of activity of such a traditional medicine and present-day Western pharmacology. Boelsma et al. [7] showed in a placebo-controlled, double-blind clinical trial that a standardized ginkgo preparation caused different effects in different subjects, which would be unacceptable to the Western way of thinking. However, their systems-biology-type of approach showed that in fact the preparation lowered peripheral blood flow in those people who had an above-average peripheral blood flow level, increased it in those who had a below average level, and in the case of the average level did not produce any effect. In other words ginkgo normalizes peripheral blood flow, a concept that does not match the reductionist approach of drug development, using the single-target, single-compound paradigm.

On the other hand, HTS may pick up well-known compounds such as adenosine and GABA in their respective receptor binding assays, thus masking possible other active compounds, but it would confirm the rationale behind the traditional use of a traditional medicine used to treat hypertension [8].

In fact the holistic ideas of traditional healthcare systems demand a holistic approach to studying their activity [4]. First, instead of trying to find an active compound, clinical trials could be considered as a way to confirm activity before trying to understand the activity. In well-established ancient healthcare systems such as in Asia, such experiments could be done in relation to current treatments. The fact that these medicines have been used for several thousand years and are still used extensively means that acute toxicity is unlikely to occur,

though long-term toxicity might be a point for some further research (see also Chapters written by Cuzzolin and Benoni, and Benoni and Cuzzolin (this volume)).

In an approach using clinical studies, systems biology enters the picture. Systems biology aims at studying an organism under different conditions without a working hypothesis. Instead one tries to measure as many parameters as possible and use multivariate analysis or other related statistical tools to asses all the data and draw conclusions from this, i.e. the hypothesis comes afterwards. These data may include physiological parameters (e.g. blood pressure, pulse), chemical parameters (using metabolomics to measure e.g. metabolites in body fluids, metabolites in a medicinal plant), the proteome and the transcriptome. Using such a holistic approach prodrugs and synergy may be found. Also new modes of action can be revealed in this way. In any case I think that the different medical systems could learn from each other and in that way make some major steps forwards and become the source of novel ideas and concepts. Combining the best of all approaches would be to the great benefit of all people's healthcare the world over.

That said, one may also wonder why the pharmaceutical industry shows such little interest in traditional medicine. Besides the fact that the above-described problems of prodrugs and synergism do not fit their present expertise for drug development, the major reason might be that of patents. It is not impossible that the activity of a traditional medicine is due to a well-known compound, e.g. GABA or adenosine, which would thus not lead to a novel active and patentable compound. Moreover, patenting of a traditional medicine might be difficult, as a patent requires some sort of innovation, something unexpected [9]. Finding antidiabetic activity in a traditional antidiabetes medicine would thus not be accepted as an innovation, and even a compound isolated for such a plant might be difficult to patent. It would be of great value to all of humanity if any industry developing a traditional medicine with a view towards an evidence-based medicine would also be given some years of protection to be able to earn back the enormous investment needed to develop an evidence-based traditional medicine.

Ginkgo may again serve as an example. There is one ginkgo preparation (see also Chapters written by Howes and Houghton, Bhatnagar, Shah, Lehotsky et al., Melzer and Seller (this volume)) that has been studied extensively in clinical trials and shown to be active. An analysis of six different preparations for sale as an over-the-counter drug on the Dutch market, one of them being an evidence-based preparation, showed that the other five had lower, and some even very low, levels of the compounds thought to be involved in the activity, but the health claims were the same as for the proven one [10, 11]. One problem facing a country such as the Netherlands that has no clear legislation regarding phytotherapy, as the government is in general unfavourably disposed towards phytomedicines, is that a de facto laissez-faire policy is established that leads to the suboptimal use of herbal medicine.

1.2 Conclusion

There is an urgent need to convince Western pharmacologists that traditional medicines can be a major source of novel medicines, as well as novel concepts, but that a different approach to studying these medicines is required.

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Chapter 2
The Chemical Diversity of Bioactive Molecules and Therapeutic Potential of Medicinal Plants

K.G. Ramawat, S. Dass and Meeta Mathur

Abstract The therapeutic use of herbs is as old as human civilization and has evolved along with it. The vast majority of people on this planet still rely on their indigenous system of medicine and use herbal drugs. The Indian and Chinese systems of medicine are well established with written records going back around 3000 years. Medicinal plant drug discovery continues to provide new and important leads against various pharmacological targets including cancer, malaria, cardiovascular diseases and neurological disorders. Interest in herbal drugs and natural medicine is undergoing a renaissance at the present time. The medicinal properties of plants are due to the presence of active principles. These bioactive secondary metabolites are synthesized by two principal pathways: shikimic acid or aromatic amino acid, and mevalonic acid. Alkaloids, phenolics and terpenoids constitute many pharmacologically active compounds. Several natural-product drugs of plant origin have either recently been approved by the US Food and Drug Administration (FDA), including arteether, galanthamine and triotopium, or are in clinical trials. Although drug discovery from medicinal plants continues to provide an important source of new drug leads, this work is constrained by the unavailability of sufficient plant material, selection and implementation of appropriate high-throughput screening bioassay and the production of bioactive compounds in large quantities. This article reviews the use of herbs in traditional systems and bioactive therapeutic molecules responsible for this activity.

Keywords Herbal drugs · Traditional medicine · Secondary metabolites · Alkaloids · Terpenes · Polyphenolics

2.1 Introduction

The world's population will be more than 7.5 billion in the next 10 to 15 years. This increase in population will occur mostly in the southern hemisphere, where 80%

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of the population still relies on a traditional system of medicine based on herbal drugs [1]. As civilizations grew from 3000 BCE onwards in Egypt, the Middle East, India and China, the uses of herbs became more sophisticated and written records were prepared. The specific plants to be used and the methods of application for particular ailments were passed down through oral history. Later on, information regarding medicinal plants was recorded in herbals [2]. Historically, herbal drugs were used as tinctures, poultices, powders and teas followed by formulations, and lastly as pure compounds. Medicinal plants or their extracts have been used by humans since time immemorial for different ailments and have provided valuable drugs such as analgesics (morphine), antitussives (codeine), antihypertensives (reserpine), cardiotonics (digoxin), antineoplastics (vinblastine and taxol) and antimalarials (quinine and artemisinin). Some of the plants which continue to be used from Mesopotamian civilization to this day are *Cedrus* spp., *Cupressus sempervirens, Glycirrhiza glabra, Commiphora wightii* and *Papaver somniferum* [1, 3, 4]. About two dozen new drugs derived from natural sources were approved by the FDA and introduced to the market during the period 2000–2005 and include drugs for cancer, neurological, cardiovascular, metabolic and immunological diseases, and genetic disorders [5]. Seven plant-derived drugs currently used clinically for various types of cancers are taxol from *Taxus* species, vinblastine and vincristine from *Catharanthus roseus*, topotecan and irinotecan from *Camptotheca accuminata*, and etoposide and teniposide from *Podophyllum peltatum* [6]. It is estimated that the worldwide market potential for herbal drugs is around US$40 billion [6]. A similar situation also exists for plant-based food additives, fragrances and biopesticides. Mostly, herbal drugs are collected from the wild, and relatively few species are cultivated. Overexploitation of plants, particularly when roots, tubers and bark are used for commercial purposes, has endangered 4,000 to 10,000 species of medicinal plants [7]. To counter overexploitation of natural resources and the consequent threats to biodiversity, alternative biotechnological methods and sustainable practices have been recommended. Several world organizations and governments have established guidelines for the collection and utilization of medicinal plants [8, 9].

2.2 Traditional Use of Medicinal Plants

Traditional medicine is the sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures used in the maintenance of health, prevention of diseases and improvement of physical and mental illness. In practice, traditional medicine refers to the following components: acupuncture (China), Ayurveda (India), Unani (Arabic countries), traditional birth attendant's medicine, mental healer's medicine, herbal medicine, and various forms of indigenous medicine. Complementary or alternative medicine refers to a broad set of healthcare practices that are not part of a country's own tradition and are not integrated into the dominant healthcare system. Traditional medicine has maintained its popularity in all regions of the developing world, and its use is rapidly spreading in industrialized countries [1]. Knowledge of plants and of healing have been

closely linked from the time of human beings' earliest social and cultural groupings. The medicine man was usually an accomplished botanist. Even in historical times, botany and medicine continued to be virtually one and the same discipline until about 1500 CE, when they began to separate from their close association, to the advantage of both sciences.

Knowledge of the medicinal plants used in the drugs of traditional systems of medicine (TSM) has been of great significance, especially as a lead for the discovery of new single-molecule medicines for modern system of medicine. To determine the chemical nature of such compounds, isolation of a substance in pure form using various separation techniques, chemical properties and spectral characteristics are a prerequisite for establishing its correct structure. Thus, medicinal plants are used in crude or purified form in the preparation of drugs in different systems. In countries like India, China and others with well-founded traditional systems of medicine, plant-based formulations occupy an important place in health management [1–10]. However, the recent broadening of the horizons of drug discovery, due to advances in instrumentation and bioinformatics (computational methods), has opened up new avenues for use of this knowledge in drug development research [2–5]. Structural novelty and new modes of action are common features of plant drugs. This has been shown by anticancer agents like vinblastine, vincristine and paclitaxel, cardiovascular agents like forskolin, anti-HIV agents like calanoid, and antihyperlipidemic agents like guggulsterones.

2.3 Ancient Systems of Medicine

2.3.1 Traditional Indian Medicine

The word Ayurveda is derived from 'Ayur', meaning life, and 'veda', meaning knowledge. Ayurveda means the science of life. It is an ancient system of health care and longevity. Ayurveda takes a holistic view of human beings, their health and illness. It aims at positive health, which has been defined as a well-balanced metabolism coupled with a healthy state of being. Disease, according to Ayurveda, can arise from the body and/or mind due to external factors or intrinsic causes. Ayurvedic treatment is aimed at the patient as an organic whole and treatment consists of the salubrious use of drugs, diet and certain practices. This doctrine was conceived when science was not developed enough to understand even the human body, let alone drug molecules [6–11].

Ayurveda, perhaps the most ancient of all medicine traditions, is probably older than traditional Chinese medicine. The origin of Ayurveda is lost in prehistoric antiquity, but its characteristic concepts appear to have matured between 2500 and 500 BCE in ancient India. The earliest references to drugs and diseases can be found in the Rigveda and Atharvaveda, dating back to 2000 BCE. Atharvaveda, comprised of 6599 hymns and 700 prose lines, is considered as the forerunner of Ayurveda.

The 'Samhitas,' or encyclopedia of medicine, were written during the postvedic era, and include 'Charak Samhita' (900 BCE), 'Sushruta Samhita' (600 BCE) and 'Ashtang Hridaya'(1000 CE). Later on, many more treatises were prepared and the use of medicinal plants is described in 'Nighantu Granthas' between the 7th and 16th centuries. The most basic concept of Ayurveda is that all living beings derive their subsistence from three essential factors (three doshas), namely vaata, pitta and kapha, which operate in unison. It believes that the human body is composed of living and non-living environments including earth, water, fire, air and space. Illness is the consequence of imbalance between the various elements, and it is the goal of treatment to restore this balance [11, 12].

Ayurvedic drugs are also attracting much attention for diseases for which there are no or inadequate drugs for treatment in modern medicine, such as metabolic and degenerative disorders. Most of these diseases have multifactorial causation, and there is a growing realization that in such conditions, a combination of drugs, acting at a number of targets simultaneously, is likely to be more effective than drugs acting at one target. Ayurvedic drugs, which are often multicomponent, have a special relevance for such conditions [12]. For various reasons, Ayurveda has not incorporated much of modern science/scientific tools. Investigation of the biological activity of multicomponent Ayurvedic drugs will bring Ayurveda into the mainstream of scientific investigations.

2.3.2 Traditional Chinese Medicine

Traditional Chinese medicine (TCM) has been in practice for more than 200 years and includes acupuncture, massage (tuina), breathing exercise (qi gong) and dietary therapy. TCM has been an integral part of China's healthcare system along with conventional Western medicine. TCM products were safe and effective for the treatment of many human diseases before Western medicine was introduced in China. Famous texts in TCM include the *Yellow Emperor's Inner Classic* (Hung Di Nei Jing; ~200 BCE to 100 CE), *Divine Husband-man's Classic of Materia Medica* (Shen Nong Ben Cao Jing; 25-220 AD) and cold-induced disorders (Shang han Lun; 220 AD). The most complete reference to Chinese herbal prescriptions is *Chinese Materia Medica*, published in 1977. It lists nearly 6000 drugs, of which 480 are of plant origin. This ancient system of medicine, believed to be more than 5000 years old, is based on two separate theories about the natural laws that govern good health and longevity, namely 'Yin and Yang', which are in opposition to each other, and the five elements (wu xing). The five-element theory is similar to the four humours and elements of the Greeks or the three humours of Ayurveda. The five elements are earth, metal, water, wood and fire, each of which is linked to the main organ systems of the body—spleen, lungs, kidney, liver and heart, respectively. It considers that an unbalanced diet, lifestyle or environment will disrupt the body balance, which in turn manifests as symptoms of diseases. The aim of the practitioner of TCM is to restore health by removing the cause, correcting abnormal functioning,

opposing the imbalance and normalizing the flow of energy. *Angelica polymorpha* var. *sinensis, Artemesia annua, Ephedra sinica, Paeonia lactiflora, Panax ginseng, Rheum palmatum* and *Peuraria lobata* constitute the important medicinal plants of TCM [3, 13, 14].

2.3.3 Traditional Egyptian Medicine

Although Egyptian medicine dates from at least 3000 BCE, the last known and most important pharmaceutical record is the *Papyrus Ebers* (1500 BCE). Use of *Ricinus communis* seeds, *Citrilus colocynthes, Senna alexandrina* and *Prunica granatum* roots in large quantities is mentioned in the ancient Egyptian literature. These uses were later documented by the Greek physician Dioscorides (100 CE). Writings of the Greeks, such as Hippocrates (460–377 BCE) and Galen (130–200 CE), also used parts of the *Papyrus Ebers*. Therefore Greek, and ultimately modern, medicine has its origin in Egyptian or Nile Valley civilization [15].

2.3.4 Traditional Arabic Medicine

The Babylonians, Assyrians and Sumerians comprise one of the oldest civilizations, and several plants were domesticated during this early period. Several medicinal plants are mentioned in civil laws carved on stone and commissioned by the King of Babylon (1700 BCE). The Arabs established drugstores in the eighth century, and the Persian pharmacist Avicenna described all Greco-Roman medicine in his book *Canon of Medicine*. This text forms the basis of distinct Islamic healing system known today as Unani-Tibb. *Papaver somniferum* was known to the Sumerians in 4000 BCE as *hul gil* (joy plant). The most frequently used medicinal plants in the Middle East are: *Allium cepa, Astracantha gummifera, Carthamus tinctorius, Carum carvi, Ferula asafoetida, Lawsonia inermis, Papaver somniferum, Peganum harmala, Prunus dulcis, Prunica granatum, Salvadora persica, Senna alexandrina, Sesamum indicum, Trachyspermum ammi, Trigonella foenum-graecum* and *Vitis vinifera* [3, 16].

2.3.5 African, European and Other Traditional Systems of Medicine

Africa is considered the cradle of *Homo sapiens*' emergence. Though traditional African medicine is the oldest and perhaps the most diverse of all healthcare systems [3], detailed documentation on the use of medicinal plants in Africa is lacking. With rapid urbanization, traditional oral knowledge is dwindling fast, e.g. knowledge of traditional oral knowledge of the Khoisan, the Nguni and the Sotho-speaking peoples [17]. Traditional African medicine is holistic, involving both body and

mind. Famous African medicinal plants include *Acaccia senegal* (source of gum Arabic), *Aloe ferox, Aloe vera, Artemisia afra, Asplanthus linearis, Boswellia sacra, Catha edulis, Commiphora myrrha, Harpagophytum procumbens, Catharanthus roseus*, etc.

Like Africa, South American countries are also rich in biodiversity and diverse healing cultures, but information on the use of medicinal plants is sparse. The famous medicinal plants from this region are *Cinchona pubescens, Erythroxylum coca, Ilex paraguariensis, Paullinia cupana, Spilanthes acmella* and *Uncarina tomentosa*. The European healing system is believed to have originated with Hippocrates (460–377 BCE) and Aristotle (384–322 BCE). Subsequent naturalists like Theophrastus (∼300 BCE), Dioscorides (100 CE) and the pharmacist Galen (130–200 CE) recorded the use of medicinal plants. The philosophy was based on the belief that the body is composed of earth, wind, fire and water, similar to the Indian system [14]. The famous book *De Materia Medica* by the Greek physician Dioscorides was the standard reference in Europe for more than 1000 years. The use of herbal teas and decoctions is still very popular in Europe, e.g. teas prepared from *Humulus lupulus, Rosmarinum officinalis, Hypericum perforum* and *Valeriana officinalis* [14].

Though traditional and alternative medicine and its practitioners exist in Europe, it is not officially recognized and is punishable under the law in France, Italy, Spain and other countries, while it is unregulated in UK. This requires provisions in pharmacopoeias to include herbal drugs. Allopathic medicine is practiced predominantly in developed countries, and herbal drugs are categorized as food supplements and are not reimbursed by the social security system.

2.4 Exploration of Medicinal Plants

Plants are a great source of therapeutic molecules. In the early 20th century, taxonomic surveys established the identity of plants, followed by ethnomedical surveys documenting the use of plants as medicine and other uses. The identification of active principles of medicinal plants leads to the use, misuse and abuse of substances of vegetal origin. The use may be curative (e.g. vincristine and vinblastine, reserpine, ephedrine, aspirin, morphine, digoxin) or narcotic abuse (cocaine, morphine and cannabis), and misuse has made several plants endangered species, e.g. *Podophyllum hexandrum, Taxus baccata, Coptis teeta, Picrorhiza kurroa* and *Nardostachys jatamansi* [18]. This overexploitation has resulted in depletion in germplasm resources, particularly in Third World countries, and urgently warrants the development of alternative biotechnological methods for micropropagation, the study of seed and reproductive biology, and, last but not least, social awareness [11]. It is estimated that approximately 1500 plant species in India are threatened including 124 endangered species [19]. About 250,000 species of higher plants are yet to be investigated for pharmacological activity. Plants can be a source of effective remedies for Alzheimer's, Parkinson's, epilepsy, migraine, arthritis and schizophrenia. Increased demand for natural drugs has led to the domestication of several plants such as