

Sonia Malik *Editor*

Biotechnology and Production of Anti- Cancer Compounds

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*This book is affectionately dedicated
to my dear mother.*

Preface

Cancer is one of the most life-threatening diseases and a major cause of death worldwide. Plants act as an important source of anti-cancer compounds. A renaissance of public interest in plant-based products due to lesser side effects and better compatibility has led to an increased demand for anti-cancer drugs obtained from plants. To meet the ever increasing demand, plants producing anti-cancer compounds are harvested from their natural sources, which direct to their extinction. Biotechnology offers a tool to produce compounds of interest without harvesting the plants from nature. Biotechnological advancements provide the opening to make use of cells, tissue or organs of economically important plants by growing them under aseptic conditions and to genetically manipulate them to obtain the desired compounds.

This book provides up-to-date information on anti-cancer drugs obtained from plants, their market demand, value as well as the role of biotechnology in the improvement of plant-based anti-cancer compounds. Chapters discuss the recent developments and techniques to obtain anti-cancer drugs from plants, in vitro protocols for optimized production of these compounds, their mode of action, and biosynthetic pathways. Experiences and views of researchers working in this area have been shared. Future strategies and goals to find out the ways to obtain the highly demanded anti-cancer compounds in an eco-friendly, economic, and efficient way are highlighted. This book will be valuable to researchers/teachers and students working in the area of plant tissue culture, natural products, phytochemistry, pharmaceutical sciences, medicines, and drug discovery.

Sao Luís, Maranhao, Brazil

Sonia Malik

Acknowledgments

The completion of this book could not have been possible without the consistent support of my beloved husband. He encouraged me to initiate this task and helped me to accomplish it. I would like to thank my wonderful son for understanding me when I was working on this book instead of playing with him. He has been a continuous source of inspiration for me. I would like to express my deepest gratitude to my great parents, grandparents, brothers and their families for their obstinate support and love.

Above all, to the Great Almighty for his countless love and blessings. God is always there to listen to our prayers and open doors if we are humble enough to knock and have faith.

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Chapter 1

Medicinal Plants: Ethno-Uses to Biotechnology Era

Aly Farag El Sheikha

Abstract To date, medicinal plants form the backbone of primary healthcare for 70–95% of the population of the developing world. Therefore, medicinal plants help in alleviating human suffering and are widely used for traditional remedies, pharmaceutical materials, and trade. Cancer patients numbers are increasing worldwide, ranking this disease as the second disease cause of mortality for both sexes. Traditionally, medicinal plants have been used in the fight against cancer, then it is considered as the basis for medicines discovery, and nowadays more than 70% of anticancer drugs have a natural source. The biotechnological tools are necessary to select, multiply, improve, and analyze medicinal plants. This chapter highlights the history of using the medicinal plants indigenously worldwide, i.e., anticancer reservoirs and also answers to many questions, such as: Why the importance of using medicinal plants is increasing recently? What are the benefits of applying the biotechnology in medicinal plants? It then describes the new biotech technique of the traceability by using PCR-DGGE to determine the geographical origin of medicinal plants (a case study of *Physalis* fruits from four different countries) by analyzing the DNA fragments of microorganisms (yeasts) on plants. This method is based on the assumption that the microbial communities of environmental samples are unique to a geographic area.

Keywords Ethnomedicine history • Medicinal plants • Anticancer reservoirs • Benefits of biotechnology • Traceability • PCR-DGGE • Origin

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Historical Background

Since the beginning of civilization, humanity has used plant materials suited for use in meeting the necessities of life. Historical contexts of using herbs traditionally depict that various medicinal plants were in use from several centuries BC by Egyptians, Chinese, Indians, Syrians, Babylonians, and Hebrews (Seid and Aydagnehum 2013; El Sheikha 2015b).

Archeologically, the Sumerians described well-established medicinal uses for such plants as laurel, caraway, and thyme (Falodun 2010); also studies have shown that the practice of herbal medicine dates as far back as 60,000 years ago in Iraq (Leroi-Gourhan 1975). The evolution of these plant-based medicine systems primarily based on plants within a local area. The great popular medicine systems are produced by several systems within Africa, the Chinese, and Tibetan of some parts of Asia, the Ayurvedic and Unani of the Indian subcontinent, the Native American of North America, and the Amazonian of South America (Mamedov 2012).

Historically, the use of herbs and spices in food preparation developed in part as a response to the threat of food-borne pathogens. Several studies illustrate that recipes are the most highly spiced in tropical regions where pathogens are the most abundant. Furthermore, the spices with the most potent antimicrobial activity tend to be selected (Billing and Sherman 1998). It is well known in all cultures; vegetables are spiced less than meat, presumably because they are more resistant to spoilage (Sherman and Hash 2001). Flowering plants were the source of most plant medicines. Stepp (2004) cited that many of the common weeds that populate human settlements, such as nettle, dandelion, and chickweed, have medicinal properties.

Ethnomedicines Uses of Herbs Between the Past and the Present

The usage of herbs for healing is the method of medicine as old as humankind itself. Man has been in a constant struggle with the disease since time immemorial, so he does not stop the search for new sources of the drug through the environment around him, and the evidence of this are many and varied including what is in the form of written documents, preserved monuments, and even original plant medicines. Increased awareness of the importance of the use of medicinal plants in the fight against diseases as a result of several years of accumulated experience due to which man learned to pursue drugs in many parts of plants, i.e., barks, seeds, fruit bodies, and other parts. Modern science has proved the functional role of plants in the treatment of diseases, and this has been evident through the incorporation of modern drug therapy for many of the drugs of plant origin which have already been used for thousands of years by the ancient civilizations. The continuous development is witnessed by the use of medicinal plants in the treatment of diseases, as well as increased awareness of the importance of the use of natural resources in the pharmaceutical industry. That has raised significantly the ability of pharmacists and physician to cope with the growing challenges in their battle against the diseases, which seek to provide a better life for humanity (Petrovska 2012).

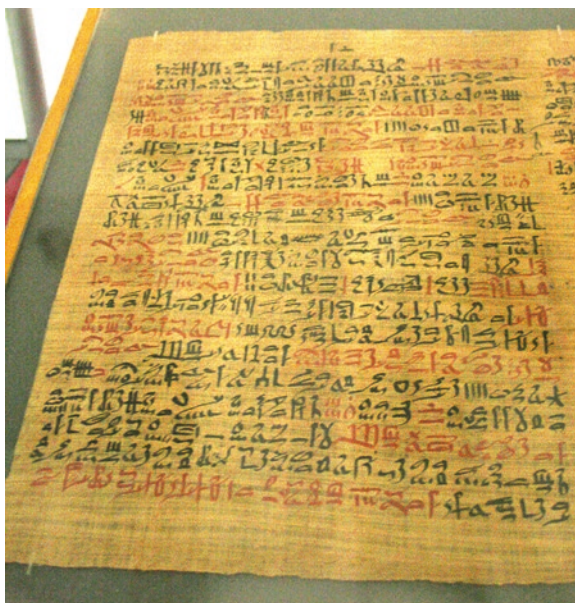
Ancient Times

Ancient peoples had acquired some knowledge of medicinal plants and used it to try to find a way to cure diseases and ease the pain of it. Predominantly, these first trials at medicine were based on speculation and superstition. They believed that evil spirits are the cause of diseases. Therefore, the use of herbs could drive them out of the body that rendered the body an unsuitable host. Usually, the healers (men or women) in the tribe were aware of the plants used in the treatment. It must not lose sight of the role of those old beliefs in this enormous development in the field of medicine (Gonsalves 2010). Methods of folk treatments throughout the world commonly used medicinal plants as part of their traditions. As following, we briefly highlight how ancient civilizations identified the medicinal plants and how to use them to heal diseases.

In Egypt

From 3000 to 6000 years ago, the ancient Egyptians have invented an efficient pharmacological collection of numerous curing materials obtained from natural resources. Nunn (1996) states: “By far the most common form of treatment recommended in the medical papyri was the use of drugs, drawn from a very wide range of animal, mineral, and vegetable materials and administered in a variety of ways. The ancient Egyptians were renowned for their skill in this respect.” The ancient Egyptians have written one of the earliest known records on Ebers Papyrus that dated to 1500 BC (Fig. 1.1), which contains information on over 850 plant medicines, including garlic, juniper, cannabis, castor bean, aloe, and mandrake (Sumner 2000). The Egyptian

Fig. 1.1 Egyptian medical papyrus of medicinal plants dating to 1550 BC (Source: https://en.wikipedia.org/wiki/Ebers_Papyrus#/media/File:PEbers_c41-bc.jpg)



physicians prescribed sedatives, analgesics, gastrointestinal disorder remedies, and medicines for urinary tract diseases and the common cold (Nunn 1996; Oakes and Gahlin 2003). Plant extracts were prepared and taken internally, applied topically, and administered by fumigation and vapor inhalation. The Egyptians are also credited with the early medicinal use of wine, castor oil, marijuana, opium, mints, and beer made from barley and wheat (Shafik and Elseesy 2003). Oakes and Gahlin (2003) point out that “The Egyptians were the first people to use some drugs that modern studies have proved would have been medicinally useful.”

In Greece

Plant-based therapeutic treatments continued to be augmented later by healthcare practitioners in ancient Greece 3000 through 1500 years ago. Only a few parts of these works have survived intact; the scientists have noted from what remains that there is a significant overlap with the Egyptian medicinal plants. Greek and Roman therapeutic practices were preserved through the writings of Hippocrates (e.g., *De herbis et curis*), especially Galen (e.g., *Therapeutics*), which were also as the headwaters for western medicine later (Robson and Baek 2009). Dioscorides, an authority on herbs who lived in the first century AD, is remarked for accumulating 24 detailed books on over 600 remedial plants and their proper uses under the title “De Materia Medica,” the earliest known name of that terminology (Sigerist 1967; Von Staden 1989).

Following those developments, additional discoveries of useful medicinal plants resulted from experimentations in several early historic cultures 1000–2000 years ago in China and India.

In China

The mythological Chinese emperor [Shennong](#) is said to have written the first [Chinese pharmacopeia](#), the “[Shennong Ben Cao Jing](#).” It lists 365 curative plants and their uses, including [hemp](#), [ephedra](#) (provided [ephedrine](#) as a drug to contemporary medicine), and [chaulmoogra](#) (one of the first effective treatments for leprosy) (Sumner 2000). Succeeding generations grown on the Shennong Bencao Jing, as in the Yaoxing Lun (Treatise on the Nature of Healing Herbs), a seventh century [Tang Dynasty](#) treatise on herbal medicine (Wu 2005).

In ancient Chinese times “traditional Chinese medicine as medicine” and “Chinese herbal medicine as pharmacy” were already described as eminent specialties. More than 85% of Chinese medical materials originate from plants, but traditional Chinese medicine practitioners also prescribe animal/insects, minerals, and crude artificial compounds. Also, the term “Chinese herbal medicine” also encompasses some ethnic herbal medicines and folk medicines in China. In Chinese herbal medicine, there are 11,146 different kinds of plants, 1581 kinds of animals/animal and insects, 80 kinds of mineral medications, and more than 50 kinds of crude chemical preparations, as well as 5000 (total one million) clinically validated herbaeous formulations. Different from other herbal medicines and Western medicines,

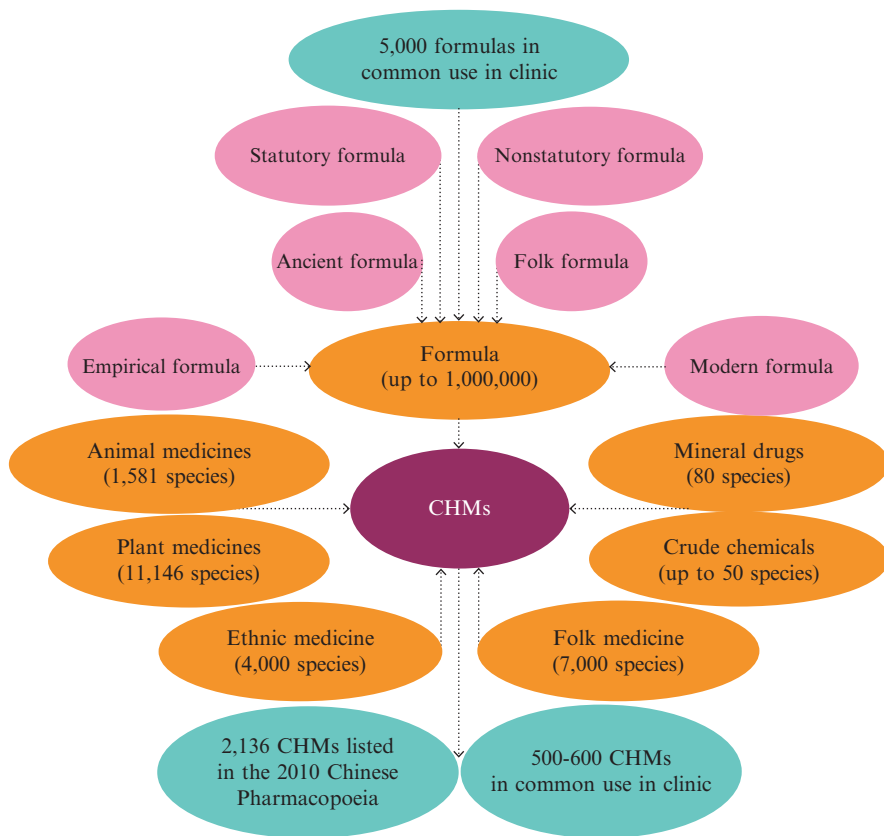


Fig. 1.2 Chinese herbal medicine: How to maximize the use of natural resources (Pan et al. 2014)

Chinese herbal medicines are often prescribed as formulas under the guidance of traditional Chinese medicines theories and practice. Each herbal medicine prescription (formula, *Fang-Ji* in Chinese) is a cocktail of many herbs tailored to the individual patient (Pan et al. 2014). It allows us to blend herbs to strengthen their benefits and reduce or eliminate any side effects when they are used each alone (Fig. 1.2).

In India

As early as 1900 BC, Ayurvedic medicine has used many medicinal plants (e.g., turmeric) (Aggarwal et al. 2007). How was the Ayurveda system basis established? It can be identified through the earliest Sanskrit writings, i.e., the Atharva Veda and Rig Veda are some of the available documents, which detail the medical knowledge (Sumner 2000). During the first millennium BC, many other curative plants, and minerals used in Ayurveda were later described by ancient Indian herbalists (e.g., Charaka and Sushruta). The Sushruta Samhita attributed to Sushruta in the sixth

century BC describes 700 medicinal plants, 64 preparations based on mineral sources, and 57 preparations from animal originate (Dwivedi and Dwivedi 2007).

Ninety percent of the 700 plant species commonly used in the Indian herbal industry are collected from the wild. The treasure of the plant and animal diversity is found in the tropical forests, but unfortunately, 50% of them have already been destroyed. Furthermore, many curative plants are on the verge of extinction. In 1997, there were many entries (427) of endangered species into the Red Data Book of India, of which 124 are endangered, 81 vulnerable, 28 considered extinct, 100 rare, and 34 insufficiently known species (Chaudhary and Singh 2010). In 2012, the Red Data Book of India described 5766 species as “endangered,” 3947 as “critically endangered,” and more than 10,000 as “vulnerable” (Fig. 1.3).

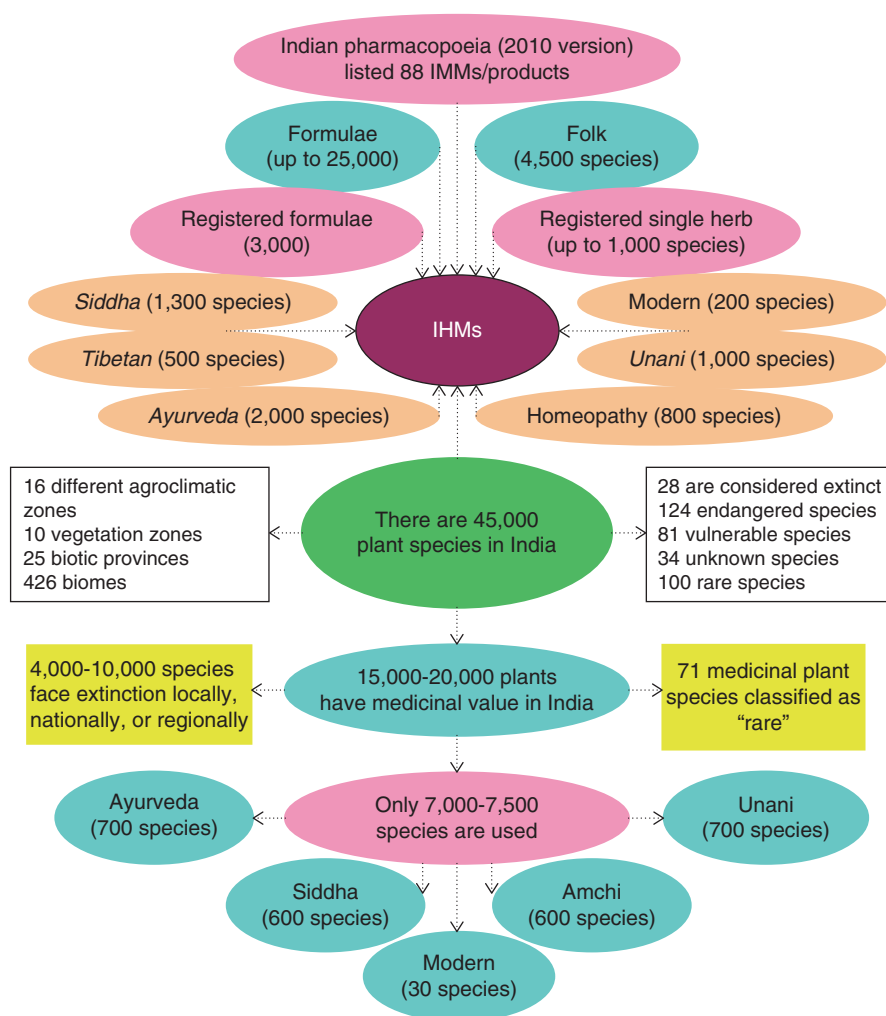


Fig. 1.3 Indian medicinal plants between the importance and the risk of extinction (Pan et al. 2014)

Middle Ages

During the Early Middle Ages, the primary source of medical knowledge in Europe and England were Benedictine monasteries. Arsdall (2002) reported that translating and copying ancient Greco-Roman and Arabic works were most of these religious scholars' efforts rather than creating essential new practices and information. The monasteries kept many Greek and Roman writings on medicine safe by hand copying of manuscripts. So these monasteries were considered as radiation centers of medical knowledge locally, and also their gardens provided many medicinal herbs, which use a simple remedy for common disorders. The traditional medicine at the same time in the home and village continued uninterrupted, supporting many wandering and settled herbalists. Hildegard of Bingen was one of the famous women in the herbal folk. A twelfth-century Benedictine nun wrote a medical text called "Causae et Curae" (Truitt 2009).

Arabic Achievements in Herbal Medicine

In the Middle Ages, the ancient Hippocratic-Greek medical know-how was adapted and improved by Arabian herbalists, pharmacologists, chemists, and physicians. Moreover, the majority of Arabs are Muslims, and Arabic culture and Islamic ideology are closely related. As such, Arabic medicine may also be called Greco-Arab or Islamic medicine. After the fall of the Roman Empire, the Arabic world became the center of scientific and medical knowledge for very long times (from 632 to 1258 CE).

During the middle ages, Arabic medicine contributed significantly to the evolution of modern medicine and pharmacy in Europe. For example, the European pharmacopoeia relied on Muslim writings and information therein until the late nineteenth century (see Fig. 1.4) (Saad et al. 2005; Azaizeh et al. 2010). The superiority of Muslims and Arabs in the field of medicine due to their implementation of the provisions of the Holy Qur'an, where serves as a good approach to both religion and life issues, and this also applies to the Sunnah of the Prophet Muhammad peace be upon him, where is the Koran full curriculum of religion and life in all its fields. The science proves every day some of the scientific facts mentioned by the Quran Karim from more than 1400 years and the rest comes.

More than 700 species of 2600 plant species in the Middle East region are noted for their use of herbs or botanical pesticides; however, only 200–250 plant species are still in use in Arab folk medicine for the treatment of different diseases (Al-Harbi et al. 1996). The western Mediterranean coastal region (from Alexandria to Sallum, Egypt) comprises 230 plant species belonging to 48 families; 89% of these species had medicinal importance, 62% of the species were common, approximately 24.9% were occasional, and 13% were scarce (Azaizeh et al. 2010). Arabic herbal medicine used in various forms include infusion, decoction, juice, syrup, roasted materials, oil, macerated plant parts, fresh salads or fruits, milky sap, poultice, and paste,

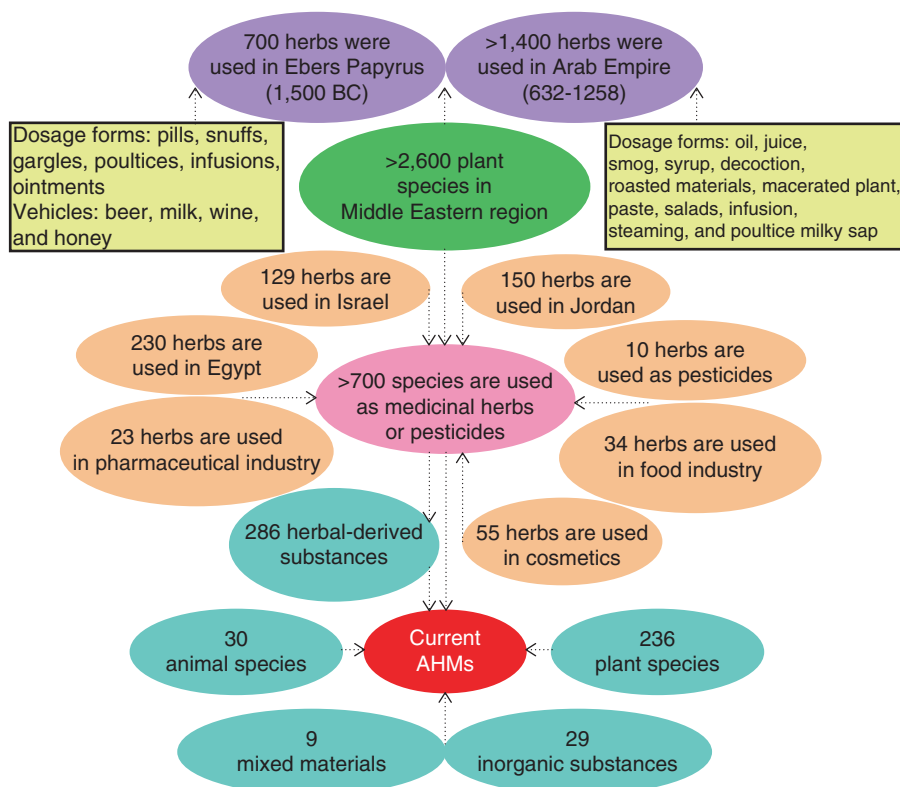


Fig. 1.4 Arabic herbal medicine: Extended history of accomplishments (Pan et al. 2014)

of which some formulations of herbal medicines are still used today. Although Arabic herbal medicine is the first choice for many people in dealing with ailments in the Middle East, most of the herbalists (i.e., those in Jordan), who acquire the expertise from their predecessors, are not adequately trained in herbal medicine (Azaizeh et al. 2010) (Fig. 1.5).

Al-Andalus was an important center for Arab herbalism between 800 and 1400, as was Baghdad. There are many works of famous Arab scholars in that period which specializes in herbal medicine. Examples of these books: “The Book of Simples” authored by Abulcasis (936–1013) in Cordoba, which is a primary source for later European herbals. “Corpus of Simples” authored by Ibn al-Baitar (1197–1248) in Malaga, a complete Arab herbal which introduced 200 new healing herbs, i.e., tamarind, nux vomica, and *Aconitum* (Castleman 2001). Avicenna wrote two books, the first is “The Canon of Medicine” in (1025), which lists 800 tested drugs, plants, and minerals (Jacquart 2008). The second one is dedicated to a discussion of the healing properties of herbs, including senna, sandalwood, nutmeg, cinnamon,



Fig. 1.5 Page from the guidebook of Arabic herbal medicine dating to 1334 CE in Arabic, describes medicinal features of cumin and dill (Source: http://en.wikipedia.org/wiki/Image:Arabic_herbal_medicine_guidebook.jpeg)

rosewater, myrrh, and rhubarb (Castleman 2001). Many other pharmacopoeia books were written in eleventh and twelfth centuries (and printed in Venice in 1491) by Abu-Rayhan Biruni and Ibn Zuhr (Avenzoar) (Krek 1979).

Modern Era

Early Modern Era

It is worth mentioning that all information about herbals was available in English for the first time in the fifteenth century. Grete Herball in 1526 published the first herbal in English. Furthermore, the two best-known herbals references in English were “The Herball or General History of Plants” by John Gerard in 1597 and “The English Physician Enlarged” by Nicholas Culpeper in 1653. Gerard’s text was a translated version of a book by the Belgian herbalist and the source of his illustrations from a German botanical work. On the other side, Culpeper’s book based on traditional medicine with astrology, magic, and folklore. The era of exploration and the Columbian Exchange introduced new medicinal plants to Europe. In the

sixteenth century, the Badianus Manuscript was an illustrated Mexican herbal written in Nahuatl and Latin (Gimmel 2008).

In contrast, the second millennium saw the beginning of a slow corrosion of the prominent position held by plants as sources of curative effects. At that time, this medical system proved that it is utterly ineffective in the face of what was called the Black Death. But Paracelsus in a century later introduced the active chemical drugs (e.g., sulfur, copper, arsenic, iron, and mercury) as an effective solution (Sonnedecker and Kremers 1986).

In the Middle Ages, especially among sixteenth and eighteenth centuries, the need for compound medications (blend of medicinal plants with drugs of animal and plant origin) was increasing, contrariwise the ancient nations used herbs primarily as simple pharmaceutical forms, i.e., macerations, infusions, and decoctions. Additionally, if the compound drug was produced from herbs, minerals, and rare animals, it was highly valued and costly (Bojadziewski 1992; Toplak Galle 2005).

During the eighteenth century, Linnaeus (1707–1788) provided a brief description and classification of the species *Plantarium* (1753). These species were named and described without taking into consideration whether some of them had previously been described. One of the greatest achievements of Linnaeus was altering the naming system from a polynomial system to a binomial one. In the polynomial system, the first word denoted the genus while the remaining phrase explained other characteristics of the plant (e.g., the willow Clusius was named *Salix pumila angustifolia antera*). But the name of species in binomial system consisted of the genus name and the species name; the genus name started with a capital letter, and the species name began with a small letter (Jančić 2002).

Turning Points in the Use of Medicinal Plants

The early nineteenth century witnessed a significant turning point on the level of systematic scientific evaluation to explain the therapeutic role of medicinal plants. It has contributed to the successive discoveries of many of the active chemical compounds found in various species of medicinal plants such as tannins, glycosides, etheric oils, vitamins, and hormones (Dervendzi 1992).

Medicinal plants were exposed to the risk of exclusion from its use as a means of therapy at the end of the nineteenth century and early twentieth century. This is attributable to the preparation processes of medicinal plants which have a great effect on their pharmacological efficacy and then leading up to non-use of medicinal plants during this period. The drying process is one of the most influential operation on the properties of medicinal plants where the risk lies in the inhibiting effect on active compounds that have a vital role in the therapeutic functions of these plant. In order to avoid the negative impact of drying, the trend has been to isolate active compounds from medicinal plants as pure compounds and use directly in the pharmaceutical industry. Early twentieth century announced yet another turning point in the therapeutic use of the medicinal plants, where research efforts went toward the utilization of the fresh medicinal plant, especially the ones with labile medicinal

substances. Besides, many efforts were invested in the study of manufacturing and cultivation conditions of medicinal plants (Lukic 1985; Kovacevic 2000).

It is evident that the active compounds extracted from herbs are considered natural products, most seamless laboratory. Therefore, it is given the fact that man is an integral part of nature, the degree of acceptance of the human body to those obtained drugs from natural sources is very high (Nelson and Cox 2005). Based on several studies (chemical, physiological, clinical), a lot of plants were restored to a pharmacy, which was forgotten before, such as *Secale cornutum*, *Filix mas*, *Punica granatum*, *Aconitum*, *Colchicum*, *Ricinus*, *Hyoscyamus*, *Stramonium*, *Opium*, and *Styrax*. There are many of examples of this kind; possibly they will push serious research into the ancient manuscripts on medicinal plants that would not be remarked out of curiosity about history but as potential sources of modern pharmacotherapy (Petrovska 2012).

Currently, almost all pharmacopoeias in the world deprive plant drugs of real medicinal value (British Pharmacopoeia Commission 2007; Council of Europe 2008; The United States Pharmacopoeial Convention 2008). There are countries (United Kingdom, Russia, Germany) that have separate herbal pharmacopoeias (Blumenthal et al. 1998; British Pharmacopoeia Commission 2007). Practically, a much higher number of unofficial drugs are always used. Their application is based on the experiences of popular medicine (folkloric medicine) or grounded on the results of recent research (conventional medicine). The use of medicinal plants is independent or in combination with synthetic drugs (complementary medicine) by the recommendation of the physician or pharmacist or through self-medication. Knowledge of the precise diagnosis of the illness is more necessary for the suitable and successfully applied therapy as medicinal plants, i.e., the pharmacological effect of their components is essential. In Germany as the major European producer and consumer of herbal preparations, rational phytotherapy is utilized grounded on applications of drugs whose efficiency depends on the dose and identified active components, and experimental and clinical tests have corroborated their effectiveness. Those preparations have been manufactured from standardized plant drug extracts, and they adhere to all requirements for pharmaceutical quality of medications (Petrovska 2012).

Importance of Medicinal Plants Has Increased Recently Why?

Why the Need Arises to Search for New Sources of Drugs?

Interestingly in recent years, there has been an evolution in the use of medicinal plants due to the side effects of synthetic drugs, lack of new pharmaceutical remedies for microbial resistance, many chronic diseases, as well as the unprecedented investment in medicinal research and development (Pan et al. 2010). Additionally, the high cost of medicines and the inability of many developing countries to purchase modern drugs have forced them to search for products in the form of medicinal plants that are proved to be cheap, efficient, safe, and culturally acceptable (Adefa and Abraha 2011).

According to the data retrieved from the World Health Organization (WHO), approximately 35,000–70,000 species has been used as drugs. This number corresponds to 14–28% of the 250,000 plants species estimated to occur around the world (Nair and Nathan 1998; Padulosi et al. 2002; Al-Sokari and El Sheikha 2015). In the global market today, much more 50 major medicaments originated from tropical plants. The variability in the biological and chemical components of plants represents a potentially limitless renewable fountain for the use in the development of novel pharmaceuticals (Mamedov 2012).

In this view, studies indicate that 25% of the modern drugs are derived from the extracts of medicinal plants. Moreover, documentation of remedial plants knowledge is incomplete as the result of a limited inventory of medicinal plants traditionally used by local people (Farnsworth 1994; El Sheikha et al. 2014).

Economic Returns for the Use of Medicinal Plants

Herbs market has expanded dramatically all over the world, an emanation of growing interest to the medical field. The income of market for sales of medicinal plants in the 1980s has climbed to about 3 billion USD/year in the North America (Glaser 1999). Also, in Canada, the use of medicinal plants has increased. Where the survey indicated that targeted 2500 people and carried out by Berger (2001) on the age groups starting at the age of 15 years to the older category, the results were 38% of the respondents are using herbal remedies, and this percentage is high compared to 1999, which was 28%. For 2007 in South America, Brazil is outstanding with 160 million USD (Tasheva and Kosturkova 2013).

Food and Drug Administration (FDA) have approved only about 1200 new drugs since 1950 (Munos 2009). As a result, in both the developing and the industrialized countries over the past 40 years, the use of herbs and its products for health objectives has increased in popularity worldwide (Humber 2002). Furthermore, with modern science/technology and ideas, the global pharmaceutical companies have begun to rediscover herbs as a possible source of new medicines and renewed their strategies to develop and discover the drugs originated from natural products (Li and Zhang 2008).

Generally in the European Union (EU), herbal products for which curative demands are made must be regulated and marketed as medications, however, those that do not make such claims be found in the cosmetic or food groups. Therefore, the need arises to unite scientific and regulatory standards that govern the marketing of herbal products, which now are progressively being to achieve this goal. At retail selling prices, the European herbal medicine market was worth over 2.8 billion USD in 1994. But at the local price level, in 1995, herbal medicinal products were estimated to be worth 5.6 billion USD (AESGP 1998). A similar increase was observed in Western Europe with 6 billion USD income for 2 years from 2003 to 2004. The sales increased in the Czech Republic by 22% from 1999 to 2001 and jumped twice in Bulgaria (Tasheva and Kosturkova 2013). The global herbal supplements and remedies market exhibited robust growth over the last decade, with

little or no significant decline on account of the recent economic recession (GIA 2016). In 2012, global sales of Chinese herbal medicine reached 83 billion USD, up more than 20% from 2011 (WHO 2013). The global herbal supplements and remedies market is forecast to reach 107 billion USD by the year 2017, spurred by growing aging population and increasing consumer awareness about general health and well-being, according to a new report from Global Industry Analysts. Additionally, the fact that herbal supplements and remedies cause little or no side effects and provide greater efficacy is also proving to be a major factor aiding market growth (GIA 2016). By 2020, the global market of medicinal plant and its products could reach 115 billion USD, with Europe the largest and the Asia-Pacific the fastest growing markets. The demand is driven by women as the main consumers of dietary supplements, by growing emphasis on healthy living and concerns over the side effects of mainstream drugs (Shetty and Rinaldi 2015).

How to Use the Herbal Medicines?

Awareness in the Use of Medicinal Plants

It is interesting that the plants that are used in food (during the cooking process, for example) as well as those that are used for therapeutic purposes to be mostly safe. In spite of the recording of the few cases of allergies as a result of the use of certain herbs (very limited number) in foods and dietary supplements, and this, of course, never reduces the high degree of safety provided by the use of medicinal plants. But everyone should not hide the fact that the effect of toxic plants may reach the level of seriousness to become deadly (e.g., poison ivy) (AHPA-ERB 2008). Perhaps history shows us this scientific truth, as Socrates was executed for 2400 years by a lethal dose of poison hemlock. To ensure the safe use of herbal products, there should be a high level of awareness and responsibility among consumers, i.e., follow label directions or the recommendation of healthcare provider for any herbal product (AHPA-ERB 2008).

Regulation and Legislation of Herbal Medicines

WHO has issued guidelines for the estimation of herbal drugs. This document covered such topics as improving procedures for clinical trials using herbal remedies, guidelines for quality specifications of plant substances and preparations, guidelines for pharmacodynamic and general pharmacological studies of herbal medications and toxicity investigations of herbal medicines, and assessing the medicinal plants research (WHO 1996). Additionally, the WHO Traditional Medicines Strategy 2014–2023 was developed to review a framework. WHO and its partners aimed at enabling (Traditional Medicine/Complementary and Alternative Medicine) to play a greater role in reducing excess morbidity and mortality, especially among impoverished populations. Many of the efforts were made at the level of traditional

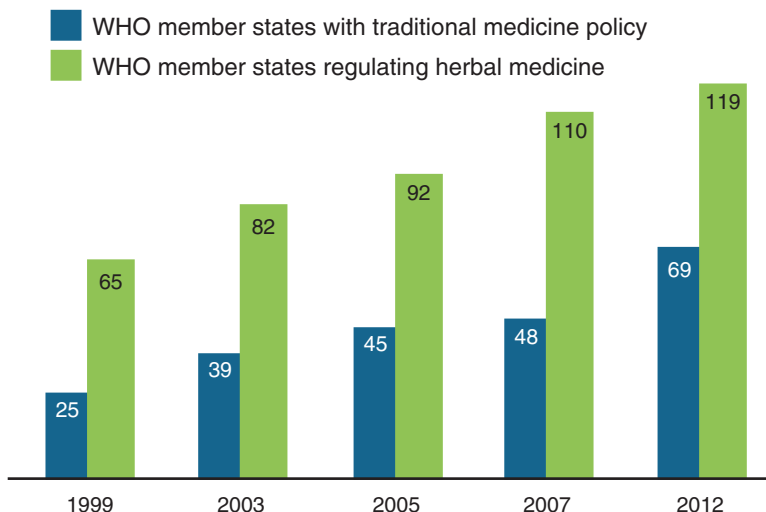


Fig. 1.6 Progress of the regulations on medicinal plants worldwide (WHO 2013)

medicines to cope with varying regulations. Each country has different rules for drug authority (WHO 2013). Over the past 15 years, the WHO has recorded a marked increase in countries with its national policies or regulations on traditional medicine about herbal medicines (see Fig. 1.6).

Based on the Council Directive 2004/24/EC (European Commission 2004), the medicinal products for human use fall under the general frame of the pharmaceutical products. It needs prior marketing approval before obtaining access to the market and investigates the requirements for the documentation of safety, quality, and efficacy, the file and expert reports (Calapai 2008). This framework has effectively been in operation by the European Agency for the Evaluation of Medicinal Plant Products (EMA) that acts as a central agency for single European drugs marketing licenses operating a Herbal Medicinal Products Working Party (HMPWP). But, some EU Member States (UK, Germany, France, Italy, etc.) have taken different techniques in reviewing herbal remedies. To differentiate between what falls under each part of herbal medicinal products, and other products, Spain has developed a draft legislation that contains the definitions of “herbal medicinal products” and “phytotraditional products.” The second one is not considered as “pharmaceutical specialties” and are therefore not classified as herbal medicinal products (IARC 2002).

In Canada, the herbal products not registered as drugs are sold as foods and are thus exempt from the medicines verification and review process, which evaluates product safety and effectiveness. In 1984, an Expert Advisory Committee on Herbs and Botanical Preparations was formed to be as advisers for the Health Protection Branch (HPB). The lists of hazardous herbal products were published by HPB, which the last version (1995) elicited a tremendous response from consumers and the herbal industry (Kozyrskyj 1997). The provincial government of British

Columbia in 2000 approved the regulations that established traditional Chinese medicine as an alternative form of essential healthcare, but the practitioners face several restrictions, including, for example, the Canadian Medicare doesn't cover the cost (Johnson 2001).

Act of Food, Drug, and Cosmetics in the USA distinguishes a product mainly by its intended use (21 Code of Federal Regulations (CFR) 201.128). Whatever the use of this product, it should be accompanied by labeling claims, as a food (including a dietary supplement), medicine (including a biological medicine), a medical device (e.g., gutta-percha) or cosmetic (FDA 2015).

Medicinal Plants Were Used Traditionally to Heal from Cancer: Why? and How?

Why People Use Herbal Medicine with Cancer?

Over the centuries, the herbal medicine has been used to heal many different health problems. The most of these uses promoted by significantly included the relaxation and cope with anxiety, depression, irritable bowel syndrome, menstrual problems, eczema, and hay fever. Concerning cancer, some studies have indicated that a significant proportion of cancer patients (60%) use medicinal plants as one of the complementary and alternative medicines (CAM) most commonly used, and it will be in parallel with conventional cancer drugs. Commonly used plants include garlic, echinacea, ginger, St John's wort, and ginseng (Langmead and Rampton 2001).

Cancer Research UK in early 2014 reported the behavior, beliefs, information, and requirements of people with cancer who take herbal medicines (Cancer Research UK 2014). The study indicated that patients mostly took herbal medicines to take back some control of their disease. They also thought that the remedies would not cause side effects.

Medicinal Plants: Cancer Remedies Between the Past and the Present

One of the major obstacles to overall public health is cancer. It is responsible for one in every four deaths in the USA alone. American Cancer Society in 2003 had estimated that there are one million new cases of invasive cancer detected with over half a million deaths from skin, squamous cell, and basal cancers. Cancer as a particular disease has a long history with herbal remedies (Hartwell 1982). Despite the suspicion that some may ask the effectiveness of these treatments as had previously been used in folklore and traditional medicine (Cragg and Newman 2005).

The natural products as secondary metabolites, which are derived from plants and microbes, have a vital contribution in the chemotherapy of cancer. The tropical

rainforests are considered as a renewable source of novel anticancer molecules for several reasons including:

- Increasing the probability of exposure some of these tropical plants at risk of extinction shortly and thus will miss the natural sources of drugs (Cox 2000).
- Great biodiversity which is characterized by tropical forests, which also make these as variety sources of natural medicines (Burslem et al. 2001).

There are some proofs which mentioned that the herbal remedies might help to prevent or relieve the symptoms of cancer or its side effects. Many researchers and through many studies conducted on lung cancer patients have been pointing out that the Chinese medicinal plants during the chemotherapy phase might be useful, but there is still a need for further studies (Cancer Research UK 2016).

Herbal Medicines: Traditional Treatment of Cancer Worldwide

Herbal drugs are enjoying widespread popularity all over the world (Almeida et al. 2006). About 85% of the world population uses medicinal plants, and the demand is increasing in developed and developing countries to prevent and heal diseases (Abramov 1996). Moreover, the investigation of herbal drugs from plants to treat cancer has been reported (Lee 1999). However, only 10% of medicinal plant species is cultivated today while the larger majority being left under wild stands threat (Cunningham 2001).

The following detailed table (Table 1.1) illustrates the medicinal plant species that are used indigenously for cancer therapy.

New Vision of Medicinal Plants by Biotechnological Lenses

How Will the Medicinal Plants Be Drugs?

Background of Knowledge

Regarding the derivative medicines from plants, it is important to keep in mind some of the conceptual differences. Plants can be used as curative resources in many ways. They can be used as herbal teas, crude extracts in pharmaceutical preparations, such as fluid, tinctures, powder, extracts, pills, and capsules when they are considered as phytopharmaceutical preparations or herbal drugs (Rates 2001).

OPS (Organización Panamericana de la Salud) was defined the medicinal plant as (1) any plant used to relieve, prevent, or treat a disease or to alter the pathological and physiological process, or (2) any plant species employed as a source of medicines (Arias 1999). Herbal medicine preparation is any manufactured medicine obtained exclusively from plants (aerial and non-aerial parts, resins, juices, oil),

Table 1.1 List of indigenous medicinal plants used for the treatment of cancer in folk medicine worldwide

Country	Plant species	Family name	Parts used	References
Jordan	<i>Narcissus tazetta</i> L.	<i>Amaryllidaceae</i>	Flowers	Talib and Mahasneh (2010)
	<i>Arum dioscoridis</i>	<i>Araceae</i>	Leaves	Ali-Shtayeh et al. (2000), Hudaib et al. (2008)
	<i>Arum hygrophilum</i>	<i>Araceae</i>	Leaves	Hudaib et al. (2008)
	<i>Arum palaestinum</i>	<i>Araceae</i>	Leaves	Said et al. (2002), Hudaib et al. (2008)
	<i>Hedera helix</i> L.	<i>Araliaceae</i>	Leaves, berries	Oran and Al-Eisawi (1998)
	<i>Inula viscosa</i> L.	<i>Asteraceae</i>	Flower heads	Talib and Mahasneh (2010)
	<i>Calendula arvensis</i> L.	<i>Asteraceae</i>	Dry flowering branches	Oran and Al-Eisawi (1998)
	<i>Anthemis pseudocotula</i>	<i>Asteraceae</i>	Flower heads	Oran and Al-Eisawi (1998)
	<i>Luffa cylindrica</i> L.	<i>Cucurbitaceae</i>	Seeds, aerial parts	Talib and Mahasneh (2010)
	<i>Arbutus andrachme</i> L.	<i>Ericaceae</i>	Leaves, fruits, roots	Said et al. (2002)
	<i>Mercurialis annua</i> L.	<i>Euphorbiaceae</i>	Leaves	Said et al. (2002)
	<i>Quercus calliprinos</i>	<i>Fagaceae</i>	Fruits, barks	Said et al. (2002)
	<i>Globularia arabica</i> L.	<i>Globulariaceae</i>	Leaves	Oran and Al-Eisawi (1998)
	<i>Laurus nobilis</i> L.	<i>Lauraceae</i>	Leaves	Said et al. (2002)
	<i>Ononis sicula</i>	<i>Leguminosae</i>	Aerial parts	Talib and Mahasneh (2010)
	<i>Anagyris foetida</i> L.	<i>Leguminosae</i>	Leaves	Oran and Al-Eisawi (1998)
	<i>Urginea maritima</i> L.	<i>Liliaceae</i>	Bulbs	Oran and Al-Eisawi (1998)
	<i>Allium cepa</i>	<i>Liliaceae</i>	Bulbs, leaves	Ali-Shtayeh et al. (2000)
	<i>Viscum cruciatum</i>	<i>Loranthaceae</i>	Pads, leaves	Ali-Shtayeh et al. (2000), Al-Qura'n (2009)
	<i>Cocculus pendulus</i>	<i>Menispermaceae</i>	Leaves, branches	Oran and Al-Eisawi (1998)
	<i>Triticum aestivum</i> L.	<i>Poaceae</i>	Shoots	Said et al. (2002)
	<i>Platanus orientalis</i> L.	<i>Polypodiaceae</i>	Leaves	Oran and Al-Eisawi (1998)
	<i>Clematis flammula</i> L.	<i>Ranunculaceae</i>	Leaves	Oran and Al-Eisawi (1998)
	<i>Zizyphus spina-christi</i> L.	<i>Rhamnaceae</i>	Fruits, leaves	Dafni et al. (2005), Hudaib et al. (2008), Saied et al. (2008)

(continued)

Table 1.1 (continued)

Country	Plant species	Family name	Parts used	References
	<i>Sarcopoterium spinosum</i> L.	Rosaceae	Leaves, seeds, roots	Hudaib et al. (2008)
	<i>Crataegus azarolus</i> L.	Rosaceae	Flowers, fruits	Said et al. (2002)
	<i>Urtica pilulifera</i> L.	Urticaceae	Leaves	Said et al. (2002)
Lebanon	<i>Bongardia chrysozonum</i> L.	Berberidaceae	Whole plant	Baydoun et al. (2015)
	<i>Carthamus tenuis</i>	Asteraceae	Seeds	Baydoun et al. (2015)
	<i>Cyclamen coum</i> Mill.	Primulaceae	Whole plant, tubers	Baydoun et al. (2015)
	<i>Clematis flammula</i> L.	Ranunculaceae	Whole plant	Baydoun et al. (2015)
	<i>Crataegus azarolus</i> L.	Rosaceae	Flowers, fruits	Said et al. (2002, 2008)
Thailand	<i>Alpinia galanga</i>	Zingiberaceae	Rhizomes	Lee and Houghton (2005)
	<i>Alpinia officinarum</i>	Zingiberaceae	Rhizomes	Lee and Houghton (2005)
	<i>Oroxylum indicum</i> L.	Bignoniaceae	Fruits	Roy et al. (2007)
	<i>Oroxylum indicum</i> L.	Bignoniaceae	Stem barks	Costa-Lotufo et al. (2005)
	<i>Rhinacanthus nasutus</i> L.	Acanthaceae	Leaves, roots	Farnsworth and Bunyapraphatsara (1992)
	<i>Dioscorea birmanica</i>	Dioscoreaceae	Rhizomes	Boonyaratankornkit and Chantapiavan (1993), Itharat et al. (2004)
	<i>Dioscorea membranacea</i>	Dioscoreaceae	Rhizomes	Itharat et al. (1999a)
	<i>Hydnophyllum formicarum</i>	Rubiaceae	Rhizomes	Itharat et al. (1999b, 2002)
	<i>Premna herbacea</i>	Verbenaceae	Rhizomes	Boonyaratankornkit and Chantapiavan (1993)
	<i>Salacia chinensis</i> L.	Celastraceae	Stems	Itharat et al. (1999b, 2002)
	<i>Siphonodon celastrineus</i>	Celastraceae	Stems, leaves	Chayamarit (1995)
	<i>Smilax corbularia</i>	Smilacaceae	Rhizomes	Boonyaratankornkit and Chantapiavan (1993)
	<i>Smilax glabra</i>	Smilacaceae	Rhizomes	Boonyaratankornkit and Chantapiavan (1993)
	<i>Suregada multiflora</i>	Euphorbiaceae	Stems	Chayamarit (1995), Itharat et al. (1999b, 2002)
Malaysia	<i>Alpinia galanga</i>	Zingiberaceae	Rhizomes	Ismail et al. (1999), Lee and Houghton (2005)
	<i>Cayratia japonica</i>	Vitaceae	Roots	Ismail et al. (1999), Lee and Houghton (2005)
	<i>Jasminum sambac</i>	Oleaceae	Roots	Ismail et al. (1999), Lee and Houghton (2005)