Chapter 2
Introduction to Medicinal Plant Safety and Efficacy

2.1 Introduction

Herbal medicine, also known as botanical medicine, herbalism, or phytotherapy, is the primary form of therapy in the all known traditional medical systems, namely, Ayurveda, Western, Chinese, Kampo, Greco-Arab and Islamic, and Unani/Tibb (Fig. 2.1) [1–3]. Ethnopharmacology has already played an important role in the development of conventional medicine and is likely to play a more significant role in the future. Herbs, fungal and bee products, as well as minerals, shells, and certain animal products represent the oldest form of healthcare natural products known to mankind. According to the World Health Organization (WHO), about 80% of the world population relies upon traditional remedies for the healthcare of its people. Many of the currently used conventional drugs are of herbal origin. Indeed, about one quarter of conventional drugs contain at least one active phytochemical. Some are made from plant extracts; others are synthesized to mimic a natural plant compound.

For therapeutic application, specific parts of the herb (aerial parts, root, leaves, fruit, flowers, and seeds) are formulated into a suitable preparation, e.g., tablets, teas, extracts, creams, or tinctures. The efficacy of herbal medicines is often described in very general terms, such as anti-inflammatory, anticancer, antiseptic (antimicrobial substances that are applied to living tissue/skin to reduce the possibility of infection), laxative (induces bowel movements or to loosen the stool), demulcent (an agent that forms a soothing film over a mucous membrane, relieving minor pain and inflammation of the membrane), antitussive (cough suppressants), or carminative (prevents formation of gas in the gastrointestinal tract or facilitates the expulsion of said gas). Unlike conventional medicines, which usually consist of a single, pure compound and are often synthetic, herbal-based medicines contain multiple phytochemicals of a single plant or a of a polyherbal mixture [1–4].

The precise number of plants to exist on earth is difficult to determine, but as of 2010, there are thought to be 300–315 thousand species. About one third of these plants are in use throughout the world. It is a well-known fact that the climatic
conditions, different places, as well as environmental factors may affect the chemical composition and concentration of herbal secondary metabolites; hence, it is not surprising that the preparation method as well as the amount of a plant product can vary in different regions. Therefore, it is vital in these instances that the crude material is assayed appropriately so that the dosage can be accurately controlled, especially where the therapeutic ratio is low (therapeutic ratio is the ratio of the dose causing toxic effects to that required for treatment). Another concern surrounding herbal medicine is the availability of wild plants for a growing market; it is feared that the limited supplies of known wild herbs are being threatened by overharvesting and habitat loss. The potential of isolating beneficial drugs from plants, however, has prompted large pharmaceutical companies to contribute to the conservation of the tropical rain forest [1–5].

The widespread use and popularity of herbal products have brought concerns and fears over professionalism of traditional caregivers and over the safety, quality, and efficacy of these products. In China and India as well as in most countries of the Arab world, herbal products (e.g., whole plants, plant extracts, tinctures, and creams) are usually sold over the counter. In contrast, herbal remedies are classified in many European countries as drugs; in the United States they are sold as dietary supplements. As discussed later in this chapter, safety assessment of herbal-based remedies has often been neglected since prolonged and apparently safe use usually is considered as an evidence of their safety. Nevertheless, evidence of the toxicity of herbal products has accumulated. This is not surprising, since herbal products are

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**Examples of Herbal-based Therapy/Prevention**

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<tr>
<th>Liver disease</th>
<th>Inflammations</th>
<th>Skin diseases</th>
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<tr>
<td><em>Silybum marianum</em>, <em>Allium cepa</em>, <em>Asparagus officinalis</em></td>
<td><em>Nigella sativa</em>, <em>Alcea setosa</em>, <em>Alchemilla vulgaris</em></td>
<td><em>Alchemilla vulgaris</em>, <em>Anchusa strigosa</em>, <em>Calotropis procera</em></td>
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<th>Pain</th>
<th>Sexual weakness</th>
<th>Cancer</th>
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<td><em>Majorana syriaca</em>, <em>Melissa officinalis</em>, <em>Myrtus communis</em></td>
<td><em>Ferula asafetida</em>, <em>Astragalus macrocarpus</em>, <em>Eruca sativa</em></td>
<td><em>Nigella sativa</em>, <em>Allium cepa</em>, <em>Arum palaestinum</em></td>
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<th>Kidney and urinary system</th>
<th>Digestive system</th>
<th>Diabetes</th>
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<tr>
<td><em>Ammi visnaga</em>, <em>Brassica napus</em>, <em>Glycyrrhiza glabra communis</em></td>
<td><em>Ceratonia siliqua</em>, <em>Foeniculum vulgare</em>, <em>Micromeria myrtifolia</em></td>
<td><em>Trigonella Foenum-gaecum</em>, <em>Achillea millefolium</em>, <em>Allium cepa</em></td>
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**Fig. 2.1** Examples of commonly used medicinal plants in the prevention and treatment of selected diseases.
complex mixtures of secondary metabolites, many of which are potentially toxic (e.g., hepatotoxic and nephrotoxic) [1–5].

Despite these concerns and fears, there is no doubt that the use of herbals and their derived products will be gradually accepted in the mainstream of conventional medicine. A teamwork among ethnobotanists, ethnopharmacologists, physicians, and phytochemists is essential for the fruitful outcome on medicinal plants research. The ethnopharmacologists will play a more effective role in studying the rationale for the presence of different combinations of activities in individual medicinal plants as well as in the compound formulations, while the phytochemists’ role will slightly shift toward the standardization of medicinal plants and their products.

2.2 Historical Aspects

As aforementioned, natural products are the ancient healthcare remedies known to mankind. Hundreds of wild edible herbs, minerals, various types of water, and animal-derived preparations are utilized by traditional healers to prepare remedies for the maintenance of healthy body, soul, and spirit as well as for the treatment and prevention of all types of known diseases. Mesopotamia, Egypt, China, Persia, India, and later on the Arab and Islamic world cradled the use of natural products as a source of medicines. Hundreds of wild plants and wild and domestic animals and their by-products (e.g., milk, honey, bones, skins, and tusks) built the main source of ingredients for the preparation of all types of medicines.

Historical evidence shows that the study of herbs dates back over 4000 years to Mesopotamia (Fig. 2.2). Sumerians utilized herbal-based products (e.g., cedar oil and cypress oil, licorice, myrrh, thyme, and poppy juice) which are still in use today for the treatment of diseases ranging from coughs and colds to parasitic infections and inflammation. Some 700 herbal- and animal-based medicines are used in Egyptian medicine that dates to about 2900 B.C. Ayurveda medicine in India has been employing herbs such as turmeric possibly as early as 1900 BC. The Sushruta Samhita by Sushruta in the sixth century B.C. describes 700 medicinal plants as well as 121 preparations from minerals and animals. The Chinese Materia Medica has been extensively documented over the centuries, with the first record dating to about 1100 B.C. Greek and Roman medicinal practices formed the roots for later Greco-Arab and Islamic medical system and modern Western medicine. Theophrastus (about 300 B.C.) in his History of Plants dealt with the medicinal qualities of herbs. Dioscorides (100 A.D.) mentioned the collection, storage, and use of herbs. Galen (130–200 A.D.) wrote 30 books on these subjects. He is well known for his complex formulas used in the preparation of compound medicines, sometimes containing dozens of ingredients.

The utilization of plants for medicine changed a little in early medieval Europe. Many Greek and Roman writings on medicine, as on other subjects, were preserved by hand copying of manuscripts in monasteries. The monasteries thus tended to
become local centers of medical knowledge. Medicinal plants provided the raw materials for simple treatment of common diseases [4–8].

Herbal medicine built a central part of Arabic medicine. In the history of science, Arabic medicine, Islamic medicine, Arab-Islamic medicine, Greco-Arab medicine, or Greco-Arab and Islamic medicine are terms that refer to medicine developed during the Golden Age of Arab-Islamic civilization (seventh to fifteenth century), which extended from Spain to Central Asia and India. This civilization became the center of brilliant medical developments and innovations, as well as great achievements in astronomy, mathematics, chemistry, philosophy, and artistic culture. Arab and Muslim scholars translated and integrated scientific knowledge of other civilizations into their own. They translated classical medical texts not only from Greek but also from Persian, Indian, and Chinese sources. Arab-Islamic medicine was not simply a continuation for Greek ideas, but it was a venue for innovation and change. Medical innovations introduced by Arab and Muslim physicians included the discovery of the immune system, the introduction of microbiological science, and the separation
of pharmacological science from medicine. This synthesis resulted in a richer and universal medical system, based on scientific roles and experimentation. Medieval Greco-Arab-Islamic medicine laid the foundation of modern Western medicine (Fig. 2.2). For instance, the Arab and Muslim scholars Al-Tabari (838–870 A.D.), Al-Razi (Rhazes, 846–930 A.D.) (Fig. 2.3), Al-Zahrawi (Albucasis 936–1013 A.D.),

Fig. 2.3 Al-Razi (Rhazes, 860–930 A.D.) was chief physician at the Baghdad Hospital. He formulated the first known description of smallpox as distinguished from measles in a work known as Liber de pestilentia. His works were widely circulated in Arabic and Greek versions and were published in Latin in the fifteenth century. One of the most important citations from Avicenna concerning psychological and body diseases was “when the disease is stronger than the natural resistance of the patient, medicine is of no use. When the patient’s resistance is stronger than the disease, the physician is of no use. When the disease and the patient’s resistance are equally balanced, the physician is needed to help tilt the balance in the patients favour” (we wish to thank Jamell Anbtawi for permitting their reproduction)
Al-Biruni (973–1050 A.D.), Ibn al-Haytham (960–1040 A.D.), Ibn Sina (Avicenna, 980–1037 A.D.) (Fig. 2.4), Ibn Zuhr (Avenzoar, 1091–1161 A.D.), Ibn al-Baitar (1197–1248 A.D.), and Ibn al-Nafees (1213–1288 A.D.) are regarded as among the great medical authorities of the medieval world, physicians whose textbooks were used in European universities up to the sixteenth century. One of the most important citations from Avicenna concerning psychological and body diseases was “We have to understand that the best and effective remedy for the treatment of patients should be through the improvement of the power of the human body in order to increase its immune system, which is based on the beauty of the surroundings and letting him listen to the best music and allow his best friends to be with him” (we wish to thank Jamell Anbtawi for permitting their reproduction).

By the seventeenth century, the knowledge of herbal medicine was widely disseminated throughout Europe. In 1649, Nicholas Culpeper wrote A Physical Directory, and a few years later produced The English Physician. This respected herbal pharmacopeia was one of the first manuals that the layperson could use for healthcare, and it is still widely referred to and quoted today. The first US Pharmacopeia was published in 1820 and became the legal standard for medical compounds in 1906. It included an authoritative listing of herbal drugs, with descriptions of their properties, uses, dosages, and tests of purity [6–9].
2.3 Revival of Interest in Phytomedicine

According to the World Health Organization (WHO), about 80% of the world population relies upon traditional remedies (mainly herbs) for the healthcare of its people. Phytochemicals represented about 80% of all drugs by the middle of the nineteenth century. At the turn of the twentieth century, synthetic drugs dominated because of rapid developments in the pharmaceutical industry, though herbal medicine has never ceased. Even today, at least 25% of sold drugs are plant-derived. In addition, about 75% of plants that provide active ingredients for prescription drugs came to the attention of researchers because of their use in traditional medicine. In addition, among the 120 active compounds currently isolated from the higher plants and widely used in modern medicine today, 80% show a positive correlation between their modern therapeutic use and the traditional use of the plants from which they are derived [9–13].

The revival of the traditional medical systems has increased worldwide over the three decades, probably stimulated by the belief that these systems flourished for hundreds of years, because of their organizational strengths and because they focus primarily on natural product-based mixtures. In line with the revival of interest in the old remedies, there is also research activity on medicinal plants particularly on the biological aspects, and the impact factor of the journals publishing such research is growing with rapid rate. One can imagine the popularity of herbal medicine in the West from the fact that an American Journal of Chinese Medicine exists in the literature. There is an increasing trend in North America and Europe to incorporate the complementary and alternative medicine, particularly the herbs as an essential component in the medical curriculum.

Herbs build a substantial branch of Greco-Arab and Islamic medicine, Ayurveda, Kampo, and traditional Chinese medicine. Essentially, herbal remedies consist of portions of plants or unpurified plant extracts containing several phytochemicals which are often generally believed to act through synergistic pathways. The recent revival of public interest in herbal preparations has been attributed to several factors [9–15]. These include:

1. The belief that herbal remedies are safe
2. Dissatisfaction with the results from conventional drugs
3. Relatively high prices of prescription drugs
4. Claims on the efficacy of herbal-based remedies
5. Preference of consumers for natural therapies and a greater interest in alternative medicines
6. Erroneous belief that herbal products are superior to manufactured products
7. Research-based improvements in the quality and safety of herbal-based preparations
8. A movement toward self-medication

In addition to these factors, various advertisements in the mass media including television and radio programmers have significantly increased consumers’ awareness and given the herbal products undue respectability and credibility.
These advertisements are carefully presented to attract the different age groups of people that exist in the society. Furthermore, the marketing strategies by various producers of herbal preparations have seriously projected these products into greater limelight. For instance, a very important factor that enhanced the present popularity and widespread use of Arab herbal-based preparations is the belief that they are prepared according to the principles of Greco-Arab and Islamic medicine. In line with the revival of interest in the old remedies, there is also greater recognition of the scholarly work of the physicians of olden days. As a result, many producers and healthcare institutions of Arab-Islamic herbal medicine are named after the famous scholars like Rhazes (Fig. 2.2), Avicenna (Fig. 2.3), Al-Zahrawi, or Ibn al-Baitar [9, 14–17].

Black seeds, garlic, ginseng, ginger, gingko, St. John’s wort, and saw palmetto are a few examples of medicinal plants which are gaining popularity among modern physicians. The revival of interest in phytomedicine at the global level has been so dramatic that sales of herbal products in the world are staggering at over 100 billion dollars a year. In 2008, $4.8 billion was spent in the United States on botanical remedies, and a large center of complementary and alternative medicine has been established recently at the NIH, with heavy funding. Recently, NIH has been engaged in sponsoring studies of large clinical trials on herbs such as ginkgo and St. John’s wort. Germany is the leading country in Europe followed by France in the use of botanicals. Around three quarters of German physicians prescribe herbs. The cost of about 40% of the herbal remedies prescribed by German physicians is covered by the healthcare system [14–17].

2.4 The Status of Herbal Medicine in the Mediterranean

To evaluate the current status of Arab-Islamic herbal medicine, Saad and Said conducted a comprehensive survey covering most regions of historic Palestine [18]. Among others, they assessed the physicians and people’s attitude toward herbal medicine and their knowledge of specific therapies as well as the qualification of the traditional Palestinian herbal medicine practitioners. The main findings of this survey indicate (1) that 87% of the interviewed persons prefer herbal-based medicines over synthetic drugs. About 30% of the asked people believe that all medicinal plants are safe, while 65.5% believe that not all plants are safe. About 93% of the interviewed persons do believe that herbal-based remedies are effective. About 95% of them were content with the result of medicinal plant treatments, and 53% confirm that the herbal treatment did indeed alleviate their aliment. Noteworthy, 72% do regularly use medicinal plants at home. Almost all interviewed people as well as traditional healers do support scientific research into the safety and efficacy of medicinal plants. (2) In regard to the status of qualification of traditional practitioners, the authors found that in parallel with the increased popularity of traditional medical systems over the last four decades, the qualifications of traditional Palestinian herbal medicine practitioners seem to be improving. About 62.5% of the
interviewed practitioners claim to be highly successful in treating cases using only herbal-based remedies, and about 53% of them claim to have an academic education and half of them have more than 10 years of experience. About 70% of the interviewed practitioners report that they were able to identify the plants they use in nature and to identify different parts of the plant used to treat different diseases. Furthermore, most of healers consider diet as part of the treatment. Many of them consider media programs and written texts as an important source for their knowledge of herbal medicine. Unfortunately, there are many books about herbal medicine on the market written in Arabic by nonspecialized authors, who often employ outdated texts by medieval Islamic physicians and herbalists such as Ibn al-Baitar and al-Antaki. One of the main errors in relying on these texts is the possible misnaming of the plant species in question. It is well known that one plant can have many names, both locally and regionally; thus, the recognition of the correct species can be exceptionally problematic. Furthermore, different plant species in many cases share the same common name. Hence, misidentification of the intended plants could lead to mistreatment and could subject the patient to harmful effects. In regard to physicians’ attitudes toward herbal-based medicine, physicians were asked about their attitudes toward herbal-based preparations in general and their knowledge regarding these remedies. About 39.6% think that medicinal plants only treat very simple diseases, and only 20% of them are willing to recommend such therapies to patients with intractable or chronic diseases. Noteworthy, 43.8% would like to learn more about medicinal plants and their traditional applications, and 91% support scientific research to develop herbal medicines. About 83% believe that herb-based remedies can complement synthetic medicines, and 85% think that some herbs should be integrated with modern medicine. Furthermore, 54.2% think that their patients are interested in herbs. This study highlights the need for educational intervention and the importance of providing physicians with the ready access to evidence-based information regarding herb-based therapies [18].

2.5 Safety of Herbal Medicines

As mentioned above, in spite of the positive perception on the use of herbal medicines and alleged satisfaction with therapeutic outcomes coupled with their disappointment with conventional medicines in terms of effectiveness [19, 20], the problem of safety of herbal products continues to remain a major issue of concern. The general belief that herbal-based healthcare products are safe and devoid of side effects is untrue and misleading. Herbs have been found to be capable of producing a wide range of side reactions some of which are capable of causing serious injuries, life-threatening conditions, and even death.

There are many reasons why herbal toxicity and a wide range of undesirable or adverse reactions may occur. These include lack of pharmaceutical-level quality control at all stages of production; confusing nomenclature and inaccurate plant identification; variations in levels of active ingredients in different plant parts and
plants harvested at different times or stages of development; or the geography, weather, soil, and other conditions specific to individual plants. The complex chemical mixtures of plants and interactions with other herbs, drugs, adulterants, or contaminants, accidental or deliberate; unprofessional, unwise, or careless practitioner treatments or recommendations; or incorrect patient use all contribute to safety issues and the increasing risk of adverse reactions. Also, contamination of herbals with microorganisms and fungal toxins such as aflatoxin, with pesticides, heavy metals, and synthetic drugs, has been described. Another problem is that herbals are usually mixtures of several ingredients or plants harvested during different seasons and extracted through variable procedures, which makes the identification of both the pharmacologically active and toxic compounds difficult. In addition, as we will see later in this chapter, herbal medicines and related products are often introduced into the market without any mandatory toxicological assessments nor effective quality standards. These herbal products are continuously made available to consumers without prescription in most cases [2, 10, 13, 15].

Scientific journals have reported a wide range of side effects, particularly hepatotoxicity. Other cases including kidney disease, cardiovascular problems, dermatologic effects, and neurological effects have also been reported in the scientific literature. In some cases, adulteration, inappropriate formulation, or lack of understanding of plant and drug interactions or uses has led to adverse reactions that are life-threatening or lethal to patients. Recently, Auerbach et al., [21] reported an association between the use of traditional herbal medicine and the development of liver fibrosis among study participants in Uganda. A number of Chinese herbal medicines and other herbal medicines from different parts of the world have also been implicated in cases of poisoning. Many of them have been shown to contain toxic compounds which are capable of reacting with cellular macromolecules including DNA, causing cellular toxicity and/or genotoxicity [14, 22]. For the purpose of brevity and other obvious constraints, adverse reactions of only a few commonly used herbal medicines are described below.

*Ephedra sinica* is used in traditional medicine to treat asthma and other respiratory problems. Ephedrine, first isolated in 1887 from this plant, is added to many herbal products marketed to reduce weight and to boost energy. These products, which act as stimulants to the central nervous cardiovascular systems, have been found to cause strokes, cardiac arrhythmias, seizures, acute psychosis, myocardial infarction, and death. By 2000, more than 1200 serious side effects related to ephedra have been reported to the FDA, though the actual number of events is undoubtedly far greater. The side effects of ephedra are enhanced when combined with caffeine [14, 23].

*Aristolochia* species contain aristolochic acids, a potential nephrotoxic and carcinogenic. Consumption of aristolochic acid-containing Chinese herbal products has also been demonstrated in several studies to be associated with increased risk of urothelial cancer. *Aristolochia fangchi* was linked to the development of subacute interstitial fibrosis of the kidney referred to as “Chinese herbs nephropathy.” Several studies that confirmed genotoxic activity of aristolochic acids reported the presence of aristolochic acid-related DNA adducts in renal tissues of patients. These mutagenic adducts, when formed, are usually poorly repaired and are capable of persisting
for years in DNA. Aristolochic acids I and II have been identified in different Asian medicinal plants and were also reported to be present in anti-overweight herbal products. This has led to the ban of medicinal products containing these acids in Belgium, the United Kingdom, Canada, Australia, and Germany [14, 24–26].

*St. John’s wort* (*Hypericum perforatum*) is a popular medicinal plant used in the treatment of mild to moderate depression. Its antidepressant effects are believed to be mediated through multiple modes, such as the inhibition of monoamine oxidase, catechol-o-methyltransferase, and dopamine-hydroxylase; blocking synaptic reuptake of 5-HT, noradrenaline, dopamine, GABA, and L-glutamate; and inhibiting nitric oxide synthase and through calcium channel and phosphodiesterase blockade. It is possible that the herbs acting through multiple sites of action require less dose for the net effect, hence resulting with less side effects. Side effects reportedly associated with its use include allergic reactions, headache, dizziness, restlessness, fatigue, dry mouth, nausea, vomiting, constipation, and photosensitivity. Interaction of *St. John’s* wort with antidepressants and anticoagulants has been demonstrated, and the herbal remedy is usually not recommended in pregnancy because of its uterotonic activity [14, 27].

*Ginkgo biloba*, mainly its roots, has found widespread use in a variety of conditions. They existed in several product forms such as extracts, tea, as well as capsules and tablets that may differ in terms of content. Over 30 ginsenosides have been identified, and these compounds are being evaluated for their anti-proliferation, antitumor, and/or anti-metastasis effects. Recently, the ability of ginsenosides to regulate signaling pathways involving cell cycle, inflammatory, or growth factor pathways has been reported. The leaf extracts of ginkgo had also been found to contain active phytochemicals that were found to improve circulation and cognition. Ginkgo extracts appear to be relatively safe, although headache, dizziness, restlessness, nausea, vomiting, diarrhea, and dermal sensitivity are the most common side effects that have been observed. The ability of ginkgo to induce liver cancer in animal test model was reported recently, and genotoxic mechanisms were suggested to play some role in the carcinogenic process. Similar observations were reported in the thyroid gland, and further studies are required to determine whether the mechanisms for the ginkgo-induced thyroid tumors are also found in humans. In addition to the carcinogenic effects in the liver and thyroid, ginkgo has also been shown to be capable of inducing tumorigenesis in the nasal cavity. Furthermore, the plant has been found to inhibit platelet-activating factor and alter coagulation times. Therefore, cautious use had been advised in individuals or patients on anticoagulants therapy [14, 28, 29].

### 2.6 Safety Monitoring and Regulatory Status of Herbal Medicines

As mentioned above, the worldwide-observed popularity in acceptance and utilization of herbal remedies and related products continues to assume exponential increase. One of the main reasons for the currently witnessed popularity is probably the belief
that these medical systems have been used for hundreds of years and that natural product-based diet and herbal-based remedies are safe because they are derived from “natural” sources. The reality is that “safety” and “natural” are not synonyms. Therefore, regulatory policies on herbal medicines and products need to be standardized and strengthened on national and international levels. Relevant regulatory authorities in different countries of the world need to be proactive and continue to put in place appropriate measures to protect public health by ensuring that all herbal medicines approved for sale are safe and of suitable quality and free of potential contaminants [1–6].

Although the assessment of the safety of herbal medicines has become an important issue for consumers, regulatory authorities, and healthcare professionals, analysis of adverse events related to the use of these products is much more complex than in the case of conventional pharmaceuticals. It is also recognized that evaluation of safety is complicated by factors such as the geographical origin of plant material, different processing techniques, route of administration, and compatibility with other medicines. In addition, a single herbal medicine or medicinal plant may contain hundreds of natural constituents, and a mixed herbal medicinal product may contain several times that number. Furthermore, there is lack of the knowledge and/or poor emphasis on the importance of taxonomic botany and documentation by most manufacturers of herbal medicines. This indeed poses peculiar challenges during identification and collection of medicinal plants used for herbal remedies. In order to eliminate the confusion created by the common names, it is necessary to adopt the most commonly used binomial names (including their binomial synonyms) for medicinal plants. For example, Artemisia absinthium L., which contains an active narcotic derivative and is capable of causing CNS disorders and generalized mental deterioration, has at least 11 different common names. Seven of the common names bear no resemblance to its botanical name. This explains why it is important to provide the exact scientific name of the plant, the plant part used, and the name of the manufacturer when reporting adverse drug reactions of herbal medicines. Therefore, effective monitoring of safety of herbal medicine will require effective collaboration between botanists, phytochemists, pharmacologists, and other major stakeholders [3, 13, 18, 30, 31].

The increasing use of herbal medicines and products in developed countries coupled with the absence or weak regulation of these products in most countries and the occurrence of high-profile safety concerns have all increased the need to monitor safety and deepen the understanding of possible side effects and the potential benefits associated with the use of herbal medicines. Adverse events arising from the consumption of herbal medicines are attributable to several factors [3, 14, 18, 27, 32]. These include:

1. Contamination with toxic or hazardous substances
2. The use of the wrong species of plant by mistake
3. Adulteration of herbal products with other
4. Undeclared medicines
5. Over dosage
6. Misuse of herbal medicines by either healthcare providers or consumers
7. The use of herbal medicines concomitantly with other medicines

Safety monitoring and regulatory status of herbal medicines vary from one country to another. Depending on the regulations applying to foods and medicines, a single herb may be considered as a diet, a functional diet, a dietary supplement, or an herbal medicine in different countries. This introduces serious difficulty in the definition of the concept of herbal medicines for the purposes of national drug regulation while at the same time also confuses patients and consumers. In the United States, for example, natural products are regulated under the Dietary Supplement Health and Education Act (DSHEA) of 1994 (US Food and Drug Administration, 2012). By definition, a dietary supplement is a product that is ingested and is intended to supplement the diet and contains a “dietary ingredient.” The dietary ingredients in these products may include vitamins, minerals, herbs, or other botanicals (US Food and Drug Administration, 2011). Under the DSHEA, additional toxicity studies are generally not required if the herb has been on the market prior to 1994 (National Institute of Health (NIH) Office of Dietary Supplements, 2011). In this regard, the FDA bears the burden to prove that a herbal medicinal product or “dietary ingredient” is toxic or not safe for use. Additional major challenge in many countries is the fact that the regulatory information on herbal medicines is often not shared between regulatory authorities and safety monitoring centers [13, 18, 30, 31].

2.7 Herbal Active Compounds

Plant metabolites are classified as primary metabolites and secondary metabolites. Basic metabolism comprises all primary metabolites necessary for the cell/tissue survival and is involved in the primary biosynthesis processes of growth, regeneration, reproduction, and maintaining plant tissues. These include carbohydrates, lipids, proteins, nucleic acids, and chlorophyll which are common to all plants. On the other hand, secondary metabolites are those that occur usually only in special, differentiated cells/tissues and are not necessary for the cells/tissues themselves but play an important role for the plant as a whole. Yet, it is not only plants that produce these bioactive compounds; rather, other organisms such as bacteria, fungi, as well as sponges and other animals are also capable of producing a large number of these metabolites. Each plant family, genus, and species produces a characteristic mix of these compounds, and they can sometimes be used as taxonomic characters in classifying plants. The number of known secondary metabolites continues to assume exponential increase. Thousands of these metabolites have been identified in several classes. In general, herbal secondary metabolites are subdivided in three major classes: alkaloids, terpenoids, and phenolics. They contain numerous phytochemicals with beneficial therapeutic as well as preventive effects [33, 34].
The patterns of secondary metabolites in a single plant may vary over time as it reacts to the changing environmental conditions. Their biosynthesis can also be influenced by a variety of factors during development, in addition to stress, which makes the determination of their complete pattern essentially very difficult. Compounds that are biosynthesized under stress conditions are typically not detectable in unstressed tissues, when they are synthesized after the invasion of plants by various pests. The synthesis of secondary metabolites can occur in all plant organs, including the flowers, fruit, seeds, roots, shoots, and leaves. Some metabolites are stored in specific compartments, which may be either whole organs or specialized cell types. Within these compartments, the concentration of toxic secondary metabolites may be very high, so that they can exert an efficient defense against herbivores. Secondary metabolites can occur in the tissues as active compounds. They can also be synthesized as inactive compounds that must be transformed into active products.

Numerous scientific reports state that the role of secondary metabolites is not essential for cells/tissue in normal growth, development, and reproduction, but they rather act in defense purposes to protect a plant from any possible harm in the environmental factors and other interspecies protection. For instance, various secondary metabolites are used to attract insects for pollination (pheromones), and others are toxins used to protect against bacterial and fungal attacks. Flavonoids can protect against free radicals generated during photosynthesis. Terpenoids may attract pollinators or seed dispersers, or inhibit competing plants. Alkaloids usually ward off herbivore animals or insect attacks (phytoalexins).

So, secondary metabolites are usually synthesized in plants for particular needs that regulate their biochemical metabolism in response to the local mix of herbivores, pollinators, and microorganisms. Secondary metabolites may often be created by modified synthetic pathways from primary metabolite, or they may share substrates of primary metabolite origin (Fig. 2.5). Plants have been evolving to adapt to the environment with genetic encoding of useful and diverse synthases for secondary metabolites. In addition, recent evidence has pointed to additional roles for secondary metabolites in plant development. Although the term “secondary metabolites” perhaps infers a less important role for these phytochemicals than those involved in primary metabolism, this is not the truth. In fact, many essential and nonessential compounds in this group are found in plants, and even the so-called nonessential materials can play a crucial role in a plant’s responses against environmental stress [33, 34].

2.8 Structure and Classification Secondary Metabolites

As mentioned above, the classification of secondary metabolites consists of terpenoids, alkaloids, and phenolics. Glycosides, tannins, and saponins are part of the phenolics that are classified according to their specific structure [33, 35].
Terpenoids: Terpenoids, or isoprenoids, are a family of compounds with great structural diversity which are essential for all living organisms. Steroids, carotenoids, and gibberellic acid are just a part of this group. Terpenoids, with over than 23,000 known structures, are polymeric isoprene derivatives and synthesized from acetate via the mevalonic acid pathway. The number of units incorporated into a particular terpene serves as a basis for their classification. Many of them have pharmacological activity and are used for disease treatment both in humans and animals. Diterpenes tend to be most abundant in Lamiaceae family and have antimicrobial and antiviral properties [33].

Alkaloids: The alkaloids present a group of plant phytochemicals that contain basic nitrogen atoms. In addition to nitrogen, alkaloids may also contain sulfur, oxygen, and rarely other elements such as chlorine, phosphorus, and bromine. Alkaloids are also produced by a large variety of organisms, such as bacteria, fungi, and animals. Most of them are toxic to other organisms and have diverse pharmacological activities. The boundary between alkaloids and other nitrogen-containing natural compounds is not a clear-cut. In contrast to most other classes of phytochemicals, alkaloids are characterized by a large structural diversity, and there is no uniform classification of them. They are biosynthesized from amino acids, such as tyrosine. A typical
example is the biosynthesis of morphine that includes a phenol coupling reaction involving a benzylisoquinoline alkaloid [33, 36].

**Phenolics** are produced by almost all plants and have in common hydroxylated aromatic rings. More than 8000 different polyphenolics are identified to date. Most of them are polymerized into larger compounds such as the lignans and proanthocyanidins. In addition, phenolic acids may occur in food plants as esters or glycosides conjugated with other natural molecules such as alcohols, flavonoids, sterols, and hydroxy fatty acids. Hydroxybenzoic and hydroxycinnamic acids present two main phenolic compounds found in plants. The total amount of phenolics in tea, coffee, berries, and fruits could reach up to 1 mg per gram of fresh plant. Phenolic compounds exhibit antioxidant, anti-inflammatory, anticarcinogenic, antimicrobial, antiseptic, and anthelmintic effects [33, 37, 38]. In recent years, there is growing evidence that plant-foods polyphenols, due to their biological properties, may be effective in the treatments for various aspects of type 2 diabetes mellitus. Based on several in vitro, animal models and some human studies, plant-derived polyphenols and polyphenol-rich diet regulate carbohydrate and lipid metabolism; attenuate hyperglycemia, dyslipidemia, and insulin resistance; improve adipose tissue metabolism; and attenuate oxidative stress and stress-sensitive signaling pathways and inflammatory processes. Polyphenolic compounds can also alleviate the development of long-term diabetes complications including cardiovascular disease, neuropathy, nephropathy, and retinopathy [33, 37, 38].

Although all polyphenols have similar chemical structures, there are some distinctive differences. Based on these differences, polyphenols can be subdivided into two classes: flavonoids and non-flavonoids, like tannins [33].

**Tannins**: The name is derived from French “tanin” (tanning substance) and used for a range of plant polyphenols. Tannins are composed by a very diverse group of oligomers and polymers. They are water-soluble compounds with the exception of some high molecular weight structures and are synthesized via shikimic acid pathway. The same pathway leads to the formation of other phenolics such as isoflavones, coumarins, lignins, and aromatic amino acids. They are usually subdivided in two groups: hydrolysable tannins (that include gallotannins, ellagitannins, complex tannins) and proanthocyanidins (also known as condensed tannins). The tannins also constitute the active principles of plant-based remedies. Plant-containing tannins are used as astringents against diarrhea, a diuretic against stomach and duodenal tumors, and anti-inflammatory agents [33].

**Glycosides**: Glycosides are compounds in which a sugar is bound to another functional group via a glycosidic bond. They play numerous important roles in living organisms. Many plants store these compounds in the form of inactive glycosides, which can be activated by enzyme hydrolysis. For this reason, most glycosides can be classified as prodrugs since they remain inactive until they are hydrolyzed in the large bowel leading to the release of the aglycone, the right active compound and the sugar component, called the glycone. Many such plant glycosides are used as herbal-based remedies [33].
**Saponins** are glucosides with foaming characteristics. They consist of a polycyclic aglycones attached to one or more sugar side chains. The aglycone part, which is also called sapogenin, is either steroid or a triterpene. The foaming ability of saponins is caused by the amphipathic character of these compounds. Saponins are produced by a large number of plants. Their pharmacological activities include membrane-permeabilizing, immunostimulant, hypocholesterolaemic, and anticarcinogenic properties, and they have also been found to significantly affect growth, feed intake, and reproduction in animals. These structurally diverse compounds have also been observed to act as antioxidants, to impair the digestion of protein and the uptake of vitamins and minerals in the gut, to cause hypoglycemia, and to act as antifungal and antiviral agents (Fig. 2.6) [33].

**Flavonoids** are one of the largest nutrient families known to scientists and include over 6000 already identified family members, all coming from six anthocyanidin aglycones derived from flavylum backbone with different glycosylations and acylations. Some of the best-known flavonoids include quercetin, kaempferol, catechins, and anthocyanidins. This nutrient group is most famous for its antioxidant and anti-inflammatory effects, as well as its contribution to the pigmentation fruits and vegetables. They are one of the most widespread families of natural pigments in the plant kingdom. They are responsible for the blue, purple, red, and orange colors of many fruits and vegetables. These pigments provide color and promote health benefits to consumers due to their antioxidant capacity. Many in vitro, in vivo, as well as animal models and human clinical trials suggest that anthocyanins have anticarcinogenic and anti-inflammatory activities, provide cardiovascular disease prevention, promote obesity and diabetes control benefits, and also improve visual and brain functions. Those health benefits are mainly associated with their antioxidant effects, which clearly are influenced by the molecular mechanism related to the expression and modulation of key genes (Fig. 2.7) [33, 34].

![Fig. 2.6 Saponins and their beneficial medicinal action](image-url)
2.9 Synergistic Actions of Phytomedicines

Selective action of a drug on the particular tissue/organ system is important for the safe therapeutic use, which is usually achieved in modern therapeutics through discovering drugs acting at specific cellular receptors. However, the use of these drugs is often associated with side effects. The presence of synergistic and/or side effect-neutralizing combinations in medicinal plants is an old concept. Many scientific reports indicate that many herbal-based medicines exert their therapeutic effects through the synergistic or additive pathway of several active compounds acting at single or multiple target cells/tissue. These synergistic or additive therapeutic effects can be beneficial by eliminating or reducing side effects associated with the predominance of a single pharmaceutical compound [27, 39, 40].

As discussed in detail in Chap. 8, herbalists prefer the use of the whole herbs or their crude extracts but not the purified active phytochemicals. They argue that the mixture of phytochemicals present in a single herb or in a polyherbal formula will interact to potentiate their therapeutic effects of the herb and reduce side effects. Potentiation can be defined as positive interactions that intensify the potency of pure bioactive ingredients. Synergistic and additive effects are subsets of potentiation. Additive effects are observed when two or more compounds in a mixture interact to provide a combined effect that is equal to the sum of the effects of the single compounds. Synergistic effects occur when combinations of two or more compounds exhibit an activity that is greater than the sum of individual compounds. Potentiation can exist between two phytochemicals in the same herb, two components from two different herbs, or between a phytochemical and a conventional drug. For instance, anticancer phytochemicals have been found to affect different phases of signal

![Fig. 2.7 Beneficial pharmaceutical properties of flavonoids](image-url)
transduction pathways including gene expression, cell cycle progression, proliferation, cell mortality, metabolism, and apoptosis. Combination anticancer drugs have been the mainstay of cancer treatment in the last four decades. Studies have documented synergistic anticancer effects of phytochemicals including quercetin, catechins, resveratrol, and curcumin with various conventional anticancer drugs. Furthermore, phytochemicals have been shown to overcome multiple drug resistance in tumors when used in combination with other natural products or conventional drugs.

Similar observations have been made in the field of antimicrobial research. In addition to the antimicrobial action of plant extracts and essential oils, a synergism between conventional antibiotics and medicinal plant-derived products has also been reported. However, it must be emphasized that the interactions between synthetic and natural drugs depend on several factors including pharmacokinetics and employed doses, since combinations confirmed in vitro may not have the same effect on humans. For example, a combination of carvone and penicillin shows synergistic effects against MRSA and *E. coli*. In contrast, an antagonistic effect between thymol and penicillin was detected against MRSA strains. In addition, synergistic effects were reported between plant pomegranate and thyme extracts and conventional antibiotics [27, 39, 40].

The group of Gilani [27] has reported other examples of synergistic and/or side effect-neutralizing combinations in medicinal plants. They found that acetylcholine and calcium channel blocker-like activities are abundantly present in herbs and usually coexist in most of the herbs studied. Calcium channel blockers are well known for their pharmacological use in the treatment of cardiovascular diseases, with potentials in a wide range of disorders, including asthma and cough, premature labor, diarrhea and abdominal spasms, gastric ulcers, as well as neurological disorders, such as migraine, epilepsy, depression, mood disorders, and Alzheimer’s disease. However, acetylcholine-like drugs have limited use in modern therapeutics despite the fact that acetylcholine is one of the most important neurotransmitters in our body without which life is almost impossible. This is mainly because of the brief and widespread actions of acetylcholine in the whole body leading to multiple side effects, as opposed to the localized effect when released physiologically.

### 2.10 Preparation Techniques and Administration Form of Herbal Medicines

Several techniques have been developed in traditional medicines that are still utilized by traditional herbalists to prepare herbal remedies (Fig. 2.8). The majority of these remedies are consumed orally in the form of tea or other drinks containing either diluted or concentrated plant extracts. The chemical composition of these extracts is largely dependent on the extraction method used. For instance, hot water extracts will be rich in polar components. Oil, on the other hand, is a nonpolar solvent and it is used to extract nonpolar phytochemicals. Alcohol lies somewhere in between. Other methods include the inhalation of aerosols (e.g., *Pimpinella anisum*),
essential oils (e.g., *Jasminum fruticans*), and vaporized plant juices or teas. Teas are generally produced from the various parts of the herbs through infusion or as decoctions. Heating a raw plant in a solvent not only aids in the extraction and concentration of curative substances but also acts to eliminate poisons and impurities prior to consumption.

Different techniques have been also developed for drug preparation for topical (external) applications that are currently used by herbalists. These include essential oils, salves, oils, balms, creams and lotions, or poultices and compresses (Fig. 2.8). In making a poultice, for instance, dry plant parts are powdered to a fine grade and combined with hot water or other liquids to create a medicinal paste or plaster. The resulting mixture is placed directly on wounds, bruises, joints, burns, insect and animal bites, rashes, swellings, wrinkles, or dermatological irritations.

A common preparation method of herbs for research purposes is alcohol/water extracts in which varying ratios of water and alcohol, usually ethanol and water, are mixed with the herb. In this method, fresh plants are collected, dried under shade,
and powdered to a fine grade. Then, 50 g of air-dried plants are added to 1 l of distilled water and boiled for 10 min. The boiled water extracts are filtered through filter paper and are freeze-dried in a lyophilizer. The freeze-dried extracts are stored at −70 °C. This method is used to extract hydrophilic substances [4, 12, 41, 42].

2.11 Therapeutic Properties of Herbal-Based Active Compounds

As aforementioned, herbs produce a wide range of secondary metabolites that are derivatives of a few biochemical precursors. These phytochemicals can have beneficial health properties in humans/animals and can be refined to produce new pharmaceuticals. Numerous herbal-derived compounds have been investigated for their potential use as sources for new drugs. Flavonoids are probably the best known of these phytochemicals due to their antioxidant and anti-inflammatory properties. To keep within the scope of this chapter, we will discuss few examples of herbal compounds and their scientific-based pharmacological properties [40–42].

Thymoquinone presents the main active principle responsible for the therapeutic properties of black seed (Nigella sativa). The seeds of this plant are known to have many health benefits and are widely used in Greco-Arab and Islamic medicine. The black seed was considered by the Prophet Mohammad (PBUH) as “the black seed can heal every disease, except death.” Avicenna (980–1037 A.D.) refers to the black seed in his The Canon of Medicine as the seed that stimulates the body’s energy and helps recovery from fatigue and dispiritedness. The seed’s oil has been used to treat skin pathological conditions such as eczema and boils and to treat cold symptoms. Numerous pharmacological and toxicological properties of the seeds have been extensively studied. A Medline search using “Nigella sativa” or “black seed” reveals more than 750 citations. These include antioxidant, anti-inflammatory, immunomodulatory, antimicrobial, antinociceptive, antidiabetic, antihistaminic, anticancer, antifertility, and hypotensive properties. In conclusion, its many uses have earned Nigella sativa the Arabic name “Habbatul barakah,” meaning the seed of blessing.

Thymoquinone has been reported to have potent antioxidant and anticancer properties in cell culture systems and animal models. It was found to inhibit a wide range of pathogenic processes (Fig. 2.9). These include inhibition of iron-dependent microsomal lipid peroxidation, cardiotoxicity induced by doxorubicin in rats, ifosfamide-induced damage in the kidney, liver injury induced with carbon tetrachloride, drug-induced toxicity, and amelioration of the drug’s anticancer activity. There are studies reporting that the anticancer effects of thymoquinone are related to its prooxidant activities. For instance, thymoquinone induces a significant release of reactive oxygen species (ROS) and inhibits the activity of aconitase, an enzyme sensitive to superoxide anion generation in human colon cancer cells and in isolated rat liver mitochondria. Furthermore, many multidrug-resistant variants of human leukemia, pancreatic adenocarcinoma, and uterine sarcoma were found to be sensitive
to thymoquinone. In addition, thymoquinone induces apoptosis through modulation of multiple targets and hence is a promising phytochemical that could be useful for the killing of many types of cancer cells. These findings are also supported by reports in prostate and other cancer cells. Thymoquinone was found to inhibit angiogenesis in vivo, through preventing tumor angiogenesis in a xenograft of human prostate cancer model in mouse and blocking human prostate tumor growth with almost no side effects. Thymoquinone inhibited the growth of prostate and colon tumors implanted in nude mice with no noticeable side effects. In colon xenografts, growth inhibition by thymoquinone was not due to the decreased proliferation but rather to the significant induction of apoptosis. However, in androgen-independent prostate tumor xenografts, the suppression of tumor growth was associated with a marked decrease in E2F-1 and induction of massive apoptosis. These results indicate that the antitumor activity or antimitotic effects could in part be due to the ability of thymoquinone to arrest cell cycle at various phases. These findings indicate a great potential into the development of new synthetic derivatives of thymoquinone as anticancer drugs [43–49].

*Oleuropein* represent the main active compound of *Olea europaea* (the olive). The olive tree is an evergreen tree or shrub native to the Mediterranean, Asia, and

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**Fig. 2.9** Different molecular targets of *N. sativa* and thymoquinone in inflammatory, cancer, and antimicrobial activities. COX cyclooxygenase, GSH reduced glutathione, GST glutathione-S-transferase, IFN-γ interferon gamma, IL interleukin, iNOS inducible nitric oxide synthase, SOD superoxide dismutase, TNF-α tumor necrosis factor alpha.
the Maghreb region. Olive leaf finds a widespread use in the Greco-Arab and Islamic medicine in the treatment and prevention of many diseases. Leaf extracts can be taken in powder, liquid concentrate, or capsule form though the fresh-picked leaf liquid extracts are quickly gaining popularity due to the broader range of healing compounds they contain [43].

The primary active compounds of olive leaf are the antioxidants oleuropein, and hydroxytyrosol, hydroxytyrosol acetate flavonoids luteolin and luteolin-glucosides. Oleuropein has a vasodilator effect, increases blood flow in the coronary arteries, and improves arrhythmia. It has proven to be a potent antioxidant, anti-inflammatory, antiviral, and antibacterial compound (Fig. 2.10). Various scientific reports indicate that oleuropein is also involved in antimicrobial activity against viruses, retroviruses, bacteria, yeasts, fungus, molds, and other parasites. Other clinical effects of oleuropein are the fortification of cellular and organism protection through macrophage response, the inhibition of plaque aggregation and eicosanoid production, and a reduction in the level of low-density lipoproteins (LDL).

One of the main scientifically supported effects of olive leaf and oleuropein is the beneficial cardiovascular activities: A strong connection between Mediterranean

Fig. 2.10 Different molecular targets of Olea europaea and oleuropein. COX cyclooxygenase, GSH reduced glutathione, GST glutathione-S-transferase, IFN-γ interferon gamma, IL interleukin, iNOS inducible nitric oxide synthase, LDL low-density lipoprotein, SOD superoxide dismutase, TNF-α tumor necrosis factor alpha
diets and lower rates of heart disease is evident through many scientific reports. The most important health-promoting substance in olive oil is oleic acid, which is a monounsaturated fatty acid. Traditional uses support olive leaf and olive oil in cardiovascular disease prevention. Indeed, there is a reduced incidence of hypertension in populations that consume olive oil-rich diet. Epidemiological data from studies in three Mediterranean countries (Italy, Greece, and Spain) as well as non-Mediterranean countries suggest a protective effect for monounsaturated fatty acids or olive oil, while non-Mediterranean countries show little or no positive effects. A diet rich in monounsaturated fatty acids (from olive oil) reduced the dosage of antihypertensive medication in patients taking these medications [43, 50, 51].

Oleuropein may play a role in the prevention of cardiovascular diseases through the inhibition of LDL oxidation. Oxidation of LDL has been identified as one of the first steps in the development of atherosclerotic lesions by promoting injury to the arterial wall. Macrophages bind to and engulf oxidized LDL that results in the production of a fatty foam cell, which, when combined with other cells, produces a fatty streak in the blood vessel. Oxidized LDL can also be taken up directly by endothelial and smooth muscle cells, leading to the formation of fatty streaks, which is the first sign of atherosclerosis. The lesions forming atherosclerotic plaques are made up of lipids, endothelial and smooth muscle cells, and extracellular matrix. The plaque environment acts as pro-inflammatory. Inflammation occurring prior to the formation of fatty streaks and atherosclerotic lesions causes alterations to the endothelial cell wall, which increases the adhesion of leukocytes, LDL cholesterol, and platelets. This contributes to the development of atherosclerosis and cardiovascular disease.

Olive leaf and their products have been found to inhibit platelet aggregation as well as the production of thromboxane A2 (a stimulator of platelet aggregation with vasodilatory effects). Also of interest is a recent study reporting that olive leaf extract inhibited both angiotensin-converting enzymes. In vitro studies have found oleanorpein and hydroxytyrosol to inhibit the production of isoprostanes, a marker of LDL oxidation. It has been suggested that phenols present in olive oil may act synergistically with these constituents to prevent LDL oxidation [43, 50, 51].

Punicalagins represent the main active phytochemical of the pomegranate (Punica granatum) (Fig. 2.11). The pomegranate has long been used in traditional folk medicine to treat a variety of diseases, including sore throat, inflammation, and rheumatism. These traditional uses of the pomegranate are common throughout the Middle East, Iran, and India, where the fruit is common. Additional traditional uses include treatment of diarrhea and colic and removal of intestinal worms in children. The fruit is also used for treating bladder disturbances, strengthening gums, and soothing mouth ulcers [43].

Pharmacological properties and potential toxicological effects of pomegranate have been extensively studied. A Medline search using pomegranate reveals more than 350 citations, including antioxidant, hormone replacement therapy, antiallergic effects, cardiovascular protection, oral hygiene, ophthalmic ointment, and an adjunct therapy to increase bioavailability of radioactive dyes during diagnostic imaging. Pomegranate-mediated antioxidant activity can be considered a means of
lowering the threshold for inflammation. Antioxidant activity, as well as suppression of inflammation, may contribute to chemotherapeutic and chemopreventive utility against cancer.

Significant progress has been made over the last two decades toward a comprehensive understanding of some of the important active compounds of pomegranate. The most abundant polyphenols in pomegranate juice are punicalagins, which have significant antioxidant activity in vitro test systems. Other phytochemicals include beta-carotene, polyphenols (e.g., catechins and gallatechins), anthocyanins (e.g., prodelphinidins, delphinidin, cyanidin, and pelargonidin), and vitamin C (0.47 mg/100 g). While multiple mechanisms reflect the pomegranate’s chemical complexity, major themes of increased apoptosis, decreased inflammation, decreased metastasis and invasion, as well as a decrease in drug resistance are evident. For instance, phytochemicals, such as ursolic acid, ellagic acid, quercetin, ellagitannins, luteolin, and apigenin, have all been associated with cancer cell apoptosis. These activities are mediated via a decrease in the activation of NF-kB, a decline in fatty acid synthase activity, inhibition of tumor necrosis factor alpha (TNF-α) production, increasing of caspase activities, and upregulation of p21 and p53 gene expression. The anti-inflammatory effects of pomegranate are mediated through the

Fig. 2.11 Different molecular targets of Punica granatum. COX cyclooxygenase, GSH reduced glutathione, GST glutathione-S-transferase, IFN-γ interferon gamma, IL interleukin, iNOS inducible nitric oxide synthase, SOD superoxide dismutase, TNF-α tumor necrosis factor alpha
inhibition of both cyclooxygenase (COX) and lysyl oxidase (LOX) enzymes and a decline in prostaglandin release from cells. Pomegranate components decrease tumor cell invasion into normal tissue and metastasis to distant sites. Mechanisms explaining these effects include inhibition of selected metalloproteinase activity, reduced vascular endothelial growth factor (VEGF) expression, and decreased focal adhesion kinase activity. Key pomegranate phytochemicals (e.g., catechins) may also reduce drug resistance through interaction with p-glycoprotein expression, relevant to potential employment of pomegranate juice or extracts as helpful adjuncts to traditional cytotoxic agents, the latter often compromised by rapid development of tumor cell resistance.

Recent studies have also begun to suggest possible synergistic interactions between aqueous and lipid phases of the fruit and between different chemicals in each phase. Though, undoubtedly, much more is still unknown than known about the pomegranate’s chemistry and medicinal potential. The beginnings of a possible use for the fruit in cancer chemoprevention and chemotherapy, largely deriving from the anti-inflammatory properties of both the aqueous and lipid phases, are in the earliest stages of being appreciated. Clinical trials with pomegranate materials, though, particularly with regard to inflammation and cancer, are still sorely lacking. Much of the work completed on pomegranate during the last decade has focused on antioxidant activity of pomegranate [43, 52, 53].

Silymarin is the main active compound of *Silybum marianum* (milk thistle). Milk thistle (Fig. 2.12), a flowering plant native to the Mediterranean region, has a long

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**Fig. 2.12** Different molecular targets of silymarin, the main active compound of *Silybum marianum*
history of use in the Greco-Arab and Islamic medicine as well as in the European folk medicine as a liver tonic. Its seeds have been used for over 2000 years to treat liver disease and protect the liver against toxins. Milk thistle is currently the most well scientifically investigated medicinal plant in the treatment of chronic or acute liver disease, as well as protecting the liver against toxicity [43].

Silymarin represent a group of hydrophobic flavonolignans that includes silybin, silidianin, and silichristine. Silymarin is found in the entire plant but is concentrated in the fruits and seeds. The seeds also contain betaine (a proven hepatoprotector) and essential fatty acids, which may contribute to silymarin’s anti-inflammatory effect. Other components include tyramine; histamine; essential oils; lipids; sugars; alkaloids; saponins; mucilages; organic acid; vitamins C, E, and K; and flavonoids such as quercetin, taxifolin, and dihydrokaempferol. Silymarin is typically administered as an encapsulated standardized extract that contain 70–80% silybin. Clinical studies have confirmed the usefulness of standardized milk thistle extracts in cases of cirrhosis, toxic liver, and other chronic liver conditions [54, 55].

Treatment of Amanita mushroom poisoning is one of the most remarkable anti-toxic properties of silymarin. This mushroom contains two extremely powerful hepatotoxins, amanitin (LD50 is 100 μg/kg body weight) and phalloidin (85 mg/kg body weight). In mice, silymarin was highly effective in preventing liver toxicity if given before or up to 10 min after Amanita toxin administration. Severe liver damage was avoided if silymarin was administered within 24 h. In another animal study with dogs, ingesting an LD50 dose of Amanita phalloides (85 mg/kg) led to mortality rate of 33%. However, 100% of the dogs survived when given silymarin 5–24 h after ingesting Amanita phalloides. Liver biopsies and liver enzyme assessments in the untreated and treated dogs revealed a significant hepatoprotective effects for silymarin. The hepatoprotective properties of silymarin in humans after ingestion of Amanita toxins have been repeatedly reported. In one study with 18 patients treated with silymarin, all patients survived except one particularly high-dose suicide. The authors concluded, “Administration of silymarin even up to 48 h after mushroom ingestion appears to be an effective measure to prevent severe liver damage in Amanita phalloides poisoning.” In a 1995 study of 41 mushroom poisoning victims, none died in the group, which included silymarin in the treatment regimen. A 1996 report made the case that silymarin may be useful even 3 days post intoxication. A family of four poisoned by Amanita mushrooms was admitted to the hospital with severe liver damage. Although all were treated with standard therapy, there was a worsening of the clinical picture until the third day, when it was decided to add silybin dihemisuccinate intravenously to the therapy. After the beginning of silybin administration, the patients showed a favorable course with a rapid resolution of the clinical picture, although the prognosis appeared severe on the basis of hepatochemical examination results. A particularly dramatic case of a very severe accidental poisoning in a 7-year-old girl resulted in her entering a hepatic coma. The authors reported the girl’s survival was due in a large part to the treatment with silymarin in combination with high doses of G-penicillin [54, 55].

Many scientific papers report about protective effects of silymarin in alcoholic liver disease. The metabolism of ethanol is primarily through conversion into acetaldehyde by three liver enzymes, namely, the catalase (CAT), the alcohol
dehydrogenases (ADH), and the microsomal ethanol-oxidizing system (MEOS). Acetaldehyde is more hepatotoxic than ethanol. Acetaldehyde produces multiple effects in the body. These include binding with proteins, glycoproteins, and membrane phospholipids, which in turn results in cellular dysfunction such as swelling, impairment of the mitochondrial electron transport chain, and upregulation of protein kinase. Maintenance of cell structure is impaired due to altered formation and function of microtubules. Acetaldehyde also increases the production of cytokines interleukin (IL)-1α, IL-6, and tumor necrosis factor alpha (TNF-α). It also promotes inflammatory responses via activation of necrosis factor kappa beta (NF-kB). Furthermore, TNF-α promotes free radical production by mitochondria, activated neutrophils, and hepatic Kupffer cells. Numerous in vitro studies of Kupffer cells and other types of immune cells investigated the effect of milk thistle or its derivatives on the formation of the nitric oxide (NO), TNF-α, prostaglandin E2 (PGE2), and leukotriene B4 (LTB4). For instance, controlled in vitro studies have demonstrated that silymarin inhibits NF-kB activation in a variety of cell lines. TNF-mediated NF-kB activation was inhibited in a dose-dependent manner. In addition, silymarin appeared to block the activation of NF-kB by phorbol ester, LPS, okadaic acid, and ceramide, partially inhibited NF-kB induction by H2O2, and was found to inhibit NF-kB activation in all cell types studied [54, 55].

Regarding the effects of silymarin on liver regeneration, silymarin (100 mg/kg) was found to enhance liver regeneration in hepatectomized rats, as shown by increased weight in treated rats as compared with controls. Proliferative activity, as measured by counting numbers of mitotic cells in prepared slides of liver tissue from hepatectomized rats, was increased in treated animals as compared with controls. The rate of DNA synthesis in rats treated with silybin following partial hepatectomy was increased 23–35% compared with controls. No change in DNA synthesis was seen in normal livers.

Milk thistle and its active compounds appear safe with relatively few side effects reported in the scientific literature. One case of severe gastroenteritis was reported following ingestion of capsules containing a variety of ingredients, including milk thistle. It is unclear whether the reaction may have been an idiosyncratic response to milk thistle or a reaction to another ingredient in the formulation. In general, the safety of both milk thistle and silymarin has been well established. No mortality or any signs of side effects were observed in a review of toxicological studies performed in various animals [43, 54, 55].

Taken together, although silymarin is safe and may have several properties that make it a potentially attractive therapy for alcoholic liver disease, such as effects on liver regeneration, lipid peroxidation, inflammation, and hepatic fibrogenesis, there are insufficient data from well-conducted clinical trials at present to routinely recommend the use of this agent for patients with alcoholic liver disease. The widespread availability for clinical trials of a standardized pure silybum/silymarin/silibin product as proposed by the National Institutes of Health will be an important first step to the systematic study of whether this herbal compound may be an effective therapy for alcoholics and other liver diseases [43, 54, 55].
2.12 Examples of Herbal Compounds and Their Pharmacological Properties

Today, there are at least 120 distinct chemical substances derived from plants that are considered as important drugs currently in use in one or more countries in the world. Some of these chemical substances are shown in the Table 2.1. Most of these herbal-derived drugs were discovered through the study of traditional medical systems, namely, the Chinese, Ayurveda, and Greco-Arab medicine (Fig. 2.13).

Table 2.1 Examples of herbal-derived drugs

<table>
<thead>
<tr>
<th>Drug/chemical</th>
<th>Action</th>
<th>Plant source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetyldigoxin</td>
<td>Cardiotonic</td>
<td>Digitalis lanata</td>
</tr>
<tr>
<td>Aescin</td>
<td>Anti-inflammatory</td>
<td>Aesculus hippocastanum</td>
</tr>
<tr>
<td>Aesculetin</td>
<td>Antidysentery</td>
<td>Fraxinus rhynchophylla</td>
</tr>
<tr>
<td>Agrimophol</td>
<td>Anthelmintic</td>
<td>Agrimonia eupatoria</td>
</tr>
<tr>
<td>Anisodamine</td>
<td>Anticholinergic</td>
<td>Anisodus tanguicus</td>
</tr>
<tr>
<td>Atropine</td>
<td>Anticholinergic</td>
<td>Atropa belladonna</td>
</tr>
<tr>
<td>Bergenin</td>
<td>Antitussive</td>
<td>Ardisia japonica</td>
</tr>
<tr>
<td>Camphor</td>
<td>Rubefacient</td>
<td>Cinnamomum camphora</td>
</tr>
<tr>
<td>Cissampeline</td>
<td>Skeletal muscle relaxant</td>
<td>Cissampelos pareira</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Local anesthetic</td>
<td>Erythroxylum coca</td>
</tr>
<tr>
<td>Codeine</td>
<td>Analgesic, antitussive</td>
<td>Papaver somniferum</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Antitumor, antigout</td>
<td>Colchicum autumnale</td>
</tr>
<tr>
<td>Convallatoxin</td>
<td>Cardiotonic</td>
<td>Convallaria majalis</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Choleretic</td>
<td>Curcuma longa</td>
</tr>
<tr>
<td>Danthron</td>
<td>Laxative</td>
<td>Cassia species</td>
</tr>
<tr>
<td>Deserpidine</td>
<td>Antihypertensive, tranquilizer</td>
<td>Rauwolfia canescens</td>
</tr>
<tr>
<td>Deslanoside</td>
<td>Cardiotonic</td>
<td>Digitalis lanata</td>
</tr>
<tr>
<td>L-Dopa</td>
<td>Anti-parkinsonism</td>
<td>Mucuna species</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>Cardiotonic</td>
<td>Digitalis purpurea</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Cardiotonic</td>
<td>Digitalis purpurea</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Sympathomimetic, antihistamine</td>
<td>Ephedra sinica</td>
</tr>
<tr>
<td>Glaucine</td>
<td>Antitussive</td>
<td>Glaucium flavum</td>
</tr>
<tr>
<td>Gossypol</td>
<td>Male contraceptive</td>
<td>Gossypium species</td>
</tr>
<tr>
<td>Hydrastine</td>
<td>Hemostatic, astringent</td>
<td>Hydrastis canadensis</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Anticancer, antitumor agent</td>
<td>Camptotheca acuminata</td>
</tr>
<tr>
<td>Kainic acid</td>
<td>Ascaricide</td>
<td>Digenea simplex</td>
</tr>
<tr>
<td>Kheltin</td>
<td>Bronchodilator</td>
<td>Ammi visnaga</td>
</tr>
<tr>
<td>Lapachol</td>
<td>Anticancer, antitumor</td>
<td>Tabebuia species</td>
</tr>
<tr>
<td>Menthol</td>
<td>Rubefacient</td>
<td>Mentha species</td>
</tr>
<tr>
<td>Methyl salicylate</td>
<td>Rubefacient</td>
<td>Gaultheria procumbens</td>
</tr>
<tr>
<td>Monocrotaline</td>
<td>Topical antitumor agent</td>
<td>Crotalaria sessiliflora</td>
</tr>
<tr>
<td>Morphine</td>
<td>Analgesic</td>
<td>Papaver somniferum</td>
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</table>

(continued)
Table 2.1 (continued)

<table>
<thead>
<tr>
<th>Drug/chemical</th>
<th>Action</th>
<th>Plant source</th>
</tr>
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<tbody>
<tr>
<td>Nicotine</td>
<td>Insecticide</td>
<td>Nicotiana tabacum</td>
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<tr>
<td>Noscapine</td>
<td>Antitussive</td>
<td>Papaver somniferum</td>
</tr>
<tr>
<td>Pachycarpine</td>
<td>Oxytocic</td>
<td>Sophora pachycarpa</td>
</tr>
<tr>
<td>Papain</td>
<td>Proteolytic, mucolytic</td>
<td>Carica papaya</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>Sympathomimetic</td>
<td>Ephedra sinica</td>
</tr>
<tr>
<td>nor-pseudoephedrine</td>
<td>Sympathomimetic</td>
<td>Ephedra sinica</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Antiarrhythmic</td>
<td>Cinchona ledgeriana</td>
</tr>
<tr>
<td>Quinine</td>
<td>Antimalarial, antipyretic</td>
<td>Cinchona ledgeriana</td>
</tr>
<tr>
<td>Reserpine</td>
<td>Antihypertensive, tranquilizer</td>
<td>Rauwolfia serpentina</td>
</tr>
<tr>
<td>Rorifone</td>
<td>Antitussive</td>
<td>Rorippa indica</td>
</tr>
<tr>
<td>Rotenone</td>
<td>Piscicide, insecticide</td>
<td>Lonchocarpus nicou</td>
</tr>
<tr>
<td>Rotundine</td>
<td>Analgesic, sedative, tranquilizer</td>
<td>Stephania sinica</td>
</tr>
<tr>
<td>Rutin</td>
<td>Treatment for capillary fragility</td>
<td>Citrus species</td>
</tr>
<tr>
<td>Salicin</td>
<td>Analgesic</td>
<td>Salix alba</td>
</tr>
<tr>
<td>Santonin</td>
<td>Ascaricide</td>
<td>Artemisia maritima</td>
</tr>
<tr>
<td>Scillaric A</td>
<td>Cardiotonic</td>
<td>Urginea maritima</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>Sedative</td>
<td>Datura species</td>
</tr>
<tr>
<td>Sennosides A, B</td>
<td>Laxative</td>
<td>Cassia species</td>
</tr>
<tr>
<td>Silymarin</td>
<td>Antihepatotoxic</td>
<td>Silybum marianum</td>
</tr>
<tr>
<td>Strychnine</td>
<td>CNS stimulant</td>
<td>Strychnos nux-vomica</td>
</tr>
<tr>
<td>Taxol</td>
<td>Antitumor agent</td>
<td>Taxus brevifolia</td>
</tr>
<tr>
<td>Tetrandrine</td>
<td>Antihypertensive</td>
<td>Stephania tetrandra</td>
</tr>
<tr>
<td>Theobromine</td>
<td>Diuretic, vasodilator</td>
<td>Theobroma cacao</td>
</tr>
<tr>
<td>Thymol</td>
<td>Topical antifungal</td>
<td>Thymus vulgaris</td>
</tr>
<tr>
<td>Topotecan</td>
<td>Antitumor, anticancer agent</td>
<td>Camptotheca acuminata</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Antitumor, antileukemic agent</td>
<td>Catharanthus roseus</td>
</tr>
</tbody>
</table>

Digitalis and the cardiac glycoside derived from the *Digitalis purpurea* (foxglove) are perhaps the most cited examples of herbal-derived drugs for the treatment of cardiovascular diseases. They are unrivaled by any synthetic or semisynthetic drugs even though they are among the most toxic group of clinically useful drugs and have unique mode of action with selective cardiotonic activity, without accompanying tachycardia. A second discovery of cardiovascular activity in medicinal plants led to the discovery of reserpine over five decades ago. Reserpine, isolated from the roots of the *Rauwolfia serpentina*, was brought to the attention of the pharmaceutical industry in 1949 by Vakil who described its use in hypertension. About 10 years later, reserpine structure was determined and its total synthesis achieved. Later on, reserpine was found to be a potent agent in treating depression and Parkinson’s disease. These findings stimulated further research, and evidence was found that reserpine depleted not only brain serotonin but also norepinephrine and dopamine. This was a major stimulus for continued research on neurotransmitter defects in depression and Parkinson’s disease. This in part laid the foundation for the development of many of
the modern psychoactive drugs and stimulated a significant interaction between researchers and drug industry.

Other examples of herbs as a source of pharmaceutical active compounds include salicylic acid (aspirin), isolated from the willow bark, which is considered as one of the most effective analgesic, antipyretic, and anti-inflammatory agents commonly used in clinical medicine. With the passage of time, multiple therapeutic uses of aspirin have been emerged, with most prevalent use as the antiplatelet/anticoagulant observed at the low dose to prevent further problems in patients who have already suffered from one heart attack. Taxol, isolated from the Taxus brevifolia (Pacific yew or Western yew), is used in treatment of various types of tumors. Vincristine isolated from Periwinkle is used to treat certain types of cancer. Quinine is an antimalarial drug isolated from Cinchona ledgeriana (Cinchona bark). For centuries, herbalists prescribed echinacea (isolated from coneflower) to fight infection.
This plant was one of the most widely prescribed medicines in the United States prior to the discovery and subsequent synthesis of antibiotics. Today, research confirms that the echinacea boosts the immune system by stimulating the production of lymphocytes. Another example of herbal-derived medicines is opium poppy (Papaver somniferum)-derived morphine, which is one of the early compounds, entered into conventional medicine, and is the humanity’s finest painkiller. Indeed, the isolation of morphine from crude opium by Serturner in 1806 stimulated so much widespread research on the vegetable drugs that Magendie was able to publish a medical formulary in 1821, which contained only pure chemical agents, hence laid the foundation for the use of single and pure compounds instead of medicinal plants and their extracts [27, 33, 35, 38–42].

Concluding Remarks

The development of effective plant-based products for improving human health is constrained by a number of issues, including a need to definitively identify relevant active components and understand synergies within them and an inability to adequately standardize replicable extracts. The body of existing phytopharmacology knowledge has led to great developments in healthcare. Many plant-derived compounds have been used as drugs, either in their original or semisynthetic form. Plant secondary metabolites can also serve as drug precursors, drug prototypes, and pharmacological probes. Indeed, many of the currently used pharmacological groups of drugs include an herb-derived prototype. Aspirin, reserpine, taxol, and tubocurarine are a few examples of drugs, which were originally discovered through the study of traditional uses and knowledge of indigenous people. Currently, there is a revival of interest in herbal medicine-based remedies at a worldwide level, and the conventional medicine is now beginning to accept the use of medicinal plants and their products once they are scientifically validated. Black seeds, ginger, ginkgo, pomegranate, milk thistle, and St. John’s wort are a few examples of medicinal plants which are gaining popularity among modern physicians and researcher, and this trend is likely to continue partly due to high cost involved in the development of patentable synthetic drugs. There is growing evidence to show that pharmacological effects of medicinal plants are potentiated through synergistic mechanisms and/or side effects neutralizing combinations. In addition to the currently observed growing interest in medicinal plants and their products, there is an increasing demand for more in depth research on biochemical and molecular action mechanisms of phytochemicals. However, it is important to mention that the vast majority of the voluminous research relating to the topics briefly reviewed above is conducted in entirely in vitro or in animal test models. Therefore, the future trends in the field of medicinal plants research must include more clinical trials. With the rapid industrialization of the planet and the loss of ethnic cultures and customs, some of this information will no doubt disappear. An abundance of ethnomedical information on plant uses can be found in the scientific literature but has not yet been compiled into a usable form. As a vast proportion of the available higher plant species have not yet been screened for biologically active compounds, drug discovery from plants should remain an

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essential component in the search for new medicines, particularly with the development of highly sensitive and versatile analytical methods. Therefore, a teamwork among ethnobotanists, ethnopharmacologists, physicians, and chemists is essential for the fruitful outcome on medicinal plants research.

References

Anti-diabetes and Anti-obesity Medicinal Plants and Phytochemicals
Safety, Efficacy, and Action Mechanisms
Saad, B.; Zaid, H.; Shanak, S.; Kadan, S.
2017, XIV, 257 p. 55 illus., 53 illus. in color., Hardcover
ISBN: 978-3-319-54101-3