



# Medicinal plants: Past history and future perspective

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**ABSTRACT**

Human societies have been in close contact with their environments since the beginning of their formation and used the ingredients of the environment to obtain food and medicine. Awareness and application of plants to prepare food and medicine have been realized through trial and error, and gradually human became able to meet his needs from his surroundings. Information about medicinal plants has long been transmitted gradually and from generation to generation, a human knowledge has gradually become complete with the formation of civilizations and the provision of more facilities. Medicinal plants are used as a medical resource in almost all cultures. Ensuring the safety, quality and effectiveness of medicinal plants and herbal drugs very recently became a key issue in industrialized and developing countries. By standardizing and evaluating the health of active plant-derived compounds, herbal drugs can help the emergence of a new era of the healthcare system to treat human diseases in the future. Awareness of traditional knowledge and medicinal plants can play a key role in the exploitation and discovery of natural plant resources. In order to maintain this knowledge, comprehensive approach and collaboration are needed to maintain historical records on medicinal plants and use these resources in favour of human beings, before they are destroyed forever. Therefore, this review was conducted to investigate and describe the process of using medicinal plants throughout history. This review focuses on the recent various important challenges in quality evaluation of medicinal plants in the authenticity, efficacy, toxicity and consistency.

**Implication for health policy/practice/research/medical education:**

Medicinal plants play a golden role not only as traditional medicine but also as trade commodities, meeting the demand of distant markets for the development of new drugs. In fact, to realize the effective integration of plants into a medical system, researchers and practitioners should be trained in both modern and traditional medicine in the use of plant compounds. In addition, to build credibility for the use of plants in conventional medicine, the empirical arguments should be converted into evidence-based arguments.

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**Introduction**

Nature is always a golden sign to show the prominent phenomena of coexistence. Natural products from plants, animals and minerals are the basis for treating human diseases (1). Medicinal plants are presently in demand and their acceptance is increasing progressively. Undoubtedly, plants play an important role by providing essential services in ecosystems. Without plants, humans and other living organisms cannot live in a way living should be. Anyway, herbals especially medicinal herbs

have constantly acted as an overall indicator of ecosystem health (2). Medicinal plants have undoubtedly been considered by human beings since ancient times. It can be said that before the history and since the early humans recognized and exploited the plants around them for use as fuel, clothing, shelter and food, they became aware of their properties more or less. Medicinal plants have been transformed into one of the oldest sciences in countries such as China, Greece, Egypt and India. In ancient Persia, plants were commonly used as a drug and disinfectant

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and aromatic agent (3). In fact, the use of medicinal plants for the treatment of diseases dates back to the history of human life, that is, since human beings have sought a tool in their environment to recover from a disease, the use of plants was their only choice of treatment (4). More than a tenth of the plant species (over 50 000 species) are used in pharmaceutical and cosmetic products. However, the distribution of medicinal plants across the world is not uniform (5,6), and medicinal herbs are mainly collected from the wildlife population. Indeed, the demand for wildlife sources has increased by 8%-15% per year in Europe, North America and Asia in recent decades (7). The term *medicinal plant* refers to a variety of plants that have medicinal properties. These plants are a rich source of compounds that can be used to develop drug synthesis (8). The parts of medicinal plants that may be used are different types of seeds, root, leaf, fruit, skin, flowers or even the whole plant. The active compounds in most parts of the medicinal plants have direct or indirect therapeutic effects and are used as medicinal agents. In the body of these plants, certain materials are produced and stored that are referred to as active compounds (substances), which have physiological effects on the living organisms (9). Human is mainly dependent on raw plant materials in order to meet medical needs to maintain health and cure diseases (10). Medicinal plants are used for treatment because they have certain properties, including synergistic actions. The constituents of the plant may interact with each other, and this interaction can be beneficial for both or adverse to either of them or eliminate the harmful effects of both. Plant-derived compounds can dramatically improve hard-to-treat illnesses, such as cancer. Plant components are also characterized by their ability to prevent the development of certain diseases. The toxicity and adverse effects of conventional and allopathic medicines have also been important factors in the sudden increase in population demands and increase in the number of herbal drug manufactures as well as a reduction in the use of chemical drugs (8).

Knowing the history of any science is effective in understanding and using that science. Hence, the historical significance of the past and present and future to medicinal herbs will continue to be addressed. In this perspective review, we have highlighted and discussed the history, current challenges, development and future outlook of using medicinal plants and their active compounds.

### History of the use of medicinal herbs

Determining the exact time of using plants as drug is very difficult. Evidence indicates that plants have been cultivated as drugs approximately 60 000 years ago (11). Scripts about medicinal plants date back to almost 5000 years ago in India, China and Egypt, and at least 2500 years in Greece and Central Asia (12). Since ancient times, people have sought to cure their own illness using

nature. As the use of animals was initially instinctive, such instinctive use was also applied to plants (13).

Given the fact that at that time there was insufficient information about the causes of the disease, useful plants for treating them, and the ways of using them for such purpose, everything was empirical. Over time, the reasons for the use of certain medicinal plants for treatment of certain diseases were discovered; consequently, the use of medicinal plants gradually rejected the empirical framework and was limited to the facts. The earliest written evidence of the use of medicinal plants for preparation of drugs has been found on a Sumerian clay slab from Nagpur dating back to nearly 5000 years ago (14). According to some inscriptions, Egyptians and Chinese who used plants as medicine since more than 27 centuries BC were among the earliest human beings who did so (15). Ancient Greek people were also familiar with the medicinal properties of some medicinal plants, and Hippocrates, the founder of Greek medicine and Aristotle, pupil of Hippocrates, used medicinal plants for the treatment of diseases. After that, Theophrastus, a Greek scientist, founded the *School of Medicinal Plants*. Then, Pedanius Dioscorides (He lived in the first century A.D), a physician and surgeon in the years 75-45 BC, wrote an encyclopedia, called *De Materia Medica*, to describe 600 therapeutic medicinal plants in the form of a series of scientific studies on medicinal plants (16-18).

### History of medicinal plants in Iran

The results of Iranian historical studies have shown that the history of the use of medicinal herbs in Iran dates back to the time of Aryan civilization from about 6500 to 7000 BC when Zarathustra referred to the properties of medicinal plants in his writings. In Zoroastrianism in Iran, a plant called *Haoma* or Ephedra (*Ephedra major* host) was considered a sacred plant (Figure 1) (17). In Iran, the traditional science of medicine and pharmacy is the result of the integration of nation's prehistorical beliefs and traditions of the early inhabitants of Mesopotamia and then the Babylonians, Assyrians, Elamites and other ancient civilizations (19,20). Iranians have long enjoyed advanced knowledge about medicinal plants and their properties. The most prominent example of this argument is *Avesta*, the sacred book of Zoroastrianism. Many sections of *Dorandiyud*, one of the 5 books of the *Avesta*,



**Figure 1.** The holy plant called *Haoma* or Ephedra (*Ephedra major* host) in Zoroastrianism.

addresses phytotherapy, medicinal plants and their use (21). But unfortunately, in the Alexander Macedonian campaign, the famous library of Alexandria was deliberately destroyed in a fire. Thus, the botanical history of Iran lacked any long-standing evidence. Later, due to the destruction of the Castles of Ismailis and the burning of their libraries by Hulagu Khan, a Mongol ruler, the rest of the books of medicinal plants that had been collected by this sect were also destroyed. Then, in the eighth and ninth centuries, Iranian physicians, including Avicenna and Razi, made great progress in Persian medicine, evidenced by great works such as Avicenna's *Canon* and Razi's *al-Hawi*. In the 13th century, Ibn al-Baitar described the properties of over 1400 plants, which he personally knew, in his book (22).

### Medicinal herbs and traditional medicine

The World Health Organization (WHO) defines traditional medicinal plants as natural plant materials which are used at least or in the absence industrial processing for the treatment of diseases at a local or regional scale (23). Traditional herbal medicine has been used in developing and developed countries for thousands of years because it is natural and causes comparatively fewer complications (24). Early medical history is consistent with the history of herbal medicine. The first books written about medicine were the first books written about plants, including the texts of the *Ebers Papyrus*, written 1500 BC, in which the names of many plants have been appeared (25). Different types of traditional drugs are widely used in Asia, Africa and Latin America to meet basic health needs. This use is growing rapidly in industrialized countries, which is often referred to as *complementary* or *alternative* medicine.

In the United States, the National Institutes of Health (NIH) uses the complementary and alternative medicine (CAM) to cover health systems, practices, and products are not presently considered to be part of conventional medicine. Across the world, among all the various traditional medical systems, traditional Chinese medicine (TCM) is currently the most popular, followed by Indian medicine. In Western countries, *Oriental Medicine* refers to Chinese, Japanese, and Korean medicines selected by immigrants from Korea, while "Asian medicine" often includes TCM, India (Ayurveda) and Tibetan medicine. Among all treatments in traditional medicine systems, medicinal plants are most frequently used (26).

### Medicinal plants and conventional medicine

Today, according to the WHO, more than 80% of the world's population rely more often on traditional drugs, mainly plants, serving as the main source of health care (27). This figure includes not only a large population of China, India and all the developing countries of the world but also many advanced countries (28). Although diseases are currently being treated more often through medicines of synthetic origin and specifically developed

in laboratories, and their definite effects in the treatment of diseases have contributed to the development of their use, the use of some medications leads to certain damages to the body. Therefore, the importance of medicinal plants and their products is increasingly recognized and the public confidence in their use is constantly strengthened (18).

Currently, the clinical, pharmaceutical and chemical studies of these traditional drugs, which are mainly derived from plants, are the basis of many early drugs such as Aspirin (from willow bark), Digoxin (from Foxglove), Morphine (from Opium poppy), Quinine (from Cinchona skin) and Pilocarpine (from Maranham Jaborandi). Currently, it is estimated that over 50% of the available drugs are somehow derived from medicinal plants (30,31). Phytotherapy is widely being used across the world on a constantly growing basis. Therefore, the global trend of synthetic compounds has turned to herbal drugs, which we can refer to it as a return to nature to prevent diseases and pains. Nature has been served as the source of medicinal herbs (32).

### Drug discovery of natural compounds

#### Traditional processes

In traditional methods, plant materials are tested for pharmaceutical purposes. If any evidence of activity is observed, the extract is fractionated, and the active compound is isolated and identified. Each step of decomposition and isolation is usually guided by biological tests, which is referred to as bioassay-guided fractionation. Figure 2 illustrates a summary of a bioassay-guided drug discovery process. Sometimes, a direct product isolation method, regardless of bioactivity, is also used, which leads to the isolation of a number of natural compounds suitable for measuring any biological activity. However, this process can be slow and inefficient, and also does not guarantee isolation of lead compounds from screening would be in chemically successful or even recordable (33).

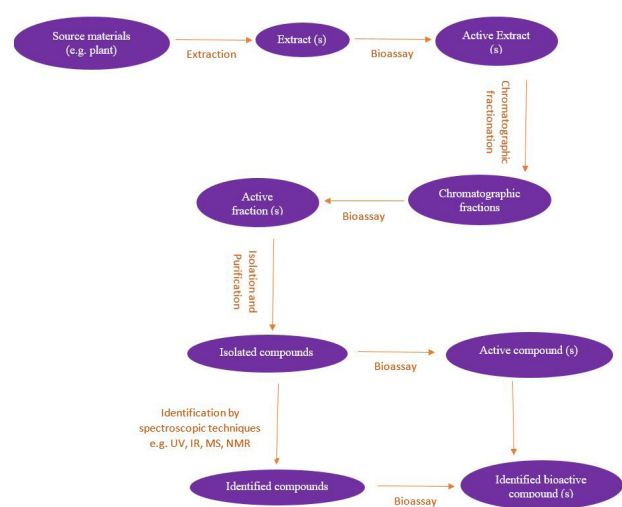


Figure 2. The traditional process of discovering natural drugs.

### Modern processes of discovering natural drugs

The methods of discovering natural drugs by using modern processes including high-throughput screening (HTS) in which, using full and robotic automation, hundreds of molecules can be screened in several tests quickly and with small amounts of compounds. In order to integrate natural products into modern HTS programs, a library of natural compounds should be founded.

While in the past, the foundation of such a library was complex, time-consuming and challenging, the conditions have improved significantly with the advent of new and advanced technologies for the isolation and identification of natural products. The best result can be obtained from a library of fully naturally identified products that enables scientists to quickly isolate lead compound for faster progression of novel drug formulation, such as full or partial synthesis, *in vivo* experiments and clinical trials (Figure 3) (33).

### Medicinal herbs in the future

Medicinal herbs have a hopeful future since there are about half a million plants around the world, most of them have not yet been studied in medical practice, and current and future studies on medical activities can be effective in treating diseases (34). The use of medicinal plants has a long history; however, the use of the whole plant or raw materials for treatment or experimentation has many drawbacks, including changes in the plant's compounds in different climates, simultaneous development of synergistic compounds that lead to adverse effects of antagonists, or other unexpected changes in bioactivity, and changes or loss of bioactivity due to the variability and accumulation, storage and preparation of raw materials; therefore, advancing towards the isolation of compounds and the use of pure substances with bioactivity, instead of the plant benefits, has certain benefits including

convenient examination of therapeutic effects and determination of toxic doses to control the quality of the therapeutic formulation (35). The beginning of the development of herbal medicines was concurrent with the development of chemistry and isolation, purification, and determination of plant compounds (36).

In the past, the drug discovery of the biological compounds from plant materials and the process of identifying the structures of active compounds from the extracts were problematic depending on the complexity of the compounds and might take weeks, months or even years. Nowadays, the rate of bioassay-guided fractionation has been significantly enhanced by the development of precision instruments such as high-performance liquid chromatography (HPLC/MS), liquid chromatography-mass spectrometry (LC/MS), magnetic field and nuclear magnetic resonance (NMR) is a recent major breakthrough for the categorization (NMR) is a recent major breakthrough for the categorization of compounds that are extremely limited in quantity in their organisms of origin (37). Despite the success of research to produce medicinal plants over the past few decades, future efforts face many challenges. The quality of the herbal product has been studied. Standardization of raw materials is an important issue for the plant industry (38).

Herbaceous plants can be easily infected during growth, processing and collection. Contamination and pollution with heavy metals are two main problems with herbal drugs. It is therefore necessary to improve the quality and quantity of bioactive compounds for the production of herbal drugs while making effort to discover more new herbal drugs (39). Due to expanding the use of natural substances around the world, the quality and safety of plant-derived medicines should be comprehensively and accurately studied issues and the traditional and the millennial beliefs about these issues cannot be surely

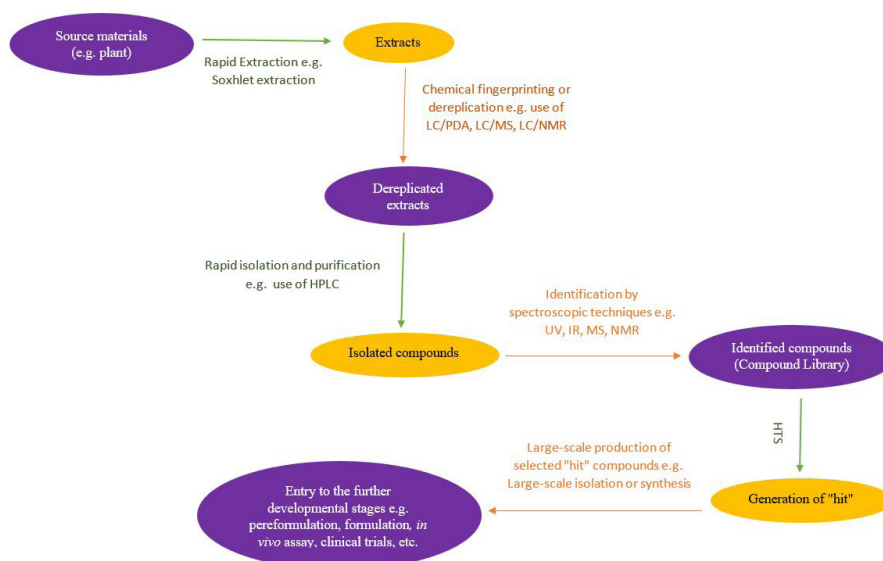


Figure 3. The modern process of discovering natural drugs.



trusted; therefore, scientific and enlightening studies are essential to obtain reliable information for the use of medicinal plants in health care (40).

On the other hand, one of the challenges facing medicinal plants is the loss of medicinal plant species due to the non-principled use of these resources. According to the International Union for Conservation of Nature, there are between 50 000 and 80 000 flowering plant species that are used for pharmaceutical purposes around the world. Among these numbers, about 15 000 species are exposed to a risk of extinction due to high harvesting and destruction of habitats (41) and 20% of their wildlife resources are decreasing due to growing human populations and excessive consumption of plants (42). Therefore, the environmental code of ethics that preserves biodiversity in the processes of exploiting natural resources to discover natural drugs should be considered (43). Good agricultural practice (GAP) for medicinal plants are planned to regulate production and ensure quality and facilitate the standardization of herbal drugs (44). GAP is an approach that uses high-quality, safe and non-contaminated (raw drugs) herbal medicines to help solve various problems (45). GAP includes comprehensive items such as environmental ecology, production locations, germplasm, cultivation, collection and quality aspects of pesticide detection, macroscopic or microscopic validation, chemical identification of active compounds, and checking of metal elements (46). Many countries seriously implement and promote the GAP. For example, in China, GAP has promoted the growth of conventional medicinal plants in areas where these plants are traditionally cultivated (47).

Although many people nowadays use herbal medicines as a constituent of primary health care, there are still many concerns about the safety and efficacy of using plants. While herbal medicines can potentially contribute to the advancement of healthcare, many major challenges need to be addressed before effective adherence of herbal medicines to traditional medicine. The lack of accurate translation and interpretation of the texts and research findings on plants by scientists around the world is one of the main challenges in this field. In fact, to realize the effective integration of plants into a medical system, researchers and practitioners should be trained in both modern and traditional medicine in the use of plant compounds. In addition, to build credibility for the use of plants in conventional medicine, the empirical arguments should be converted into evidence-based arguments. Finally, several questions about safety, accurate dose, duration of treatment, side effects, acute and chronic toxicities as well as the standardization of herbal medicines and natural products should be answered. If these issues are resolved, medicinal plants can be used as a safe, effective, and affordable form of health care.

### Conclusion and future outlook

Undoubtedly, the demand for plant-derived products has increased across the world. In the Middle East, Latin America, Africa and Asia more than 85 percent of the populations predominantly rely on traditional medicine, especially on herbal medicines, for their health care needs. About 100 million people in the European Union and in some countries as high as 90% of the population, still use traditional, complementary or herbal medicines. The herbal medicine has an increasing big market. In 2012, the whole sales of Chinese herbal medicines reached more than US\$83 billion which was 20% more than the market in 2011. It has been suggested that the whole market for all herbal supplements will reach more than US\$115 billion by 2020, which in Asia-Pacific is the fastest and in Europe is the largest growing markets. These demands are predominantly driven by women subjects by growing emphasis on concerns on the adverse effects of synthetic drugs. Therefore, investing in human resource training can be the main source of research development in order to move from production to the production of crops. The importance of research in the field of medicinal plants is felt more than ever. Some medicinal plants are the sources of adjuvant therapy in the health systems worldwide, not only to treat diseases but also to prevent them and maintain health. Despite the extensive experiences in use of medicinal plants in traditional medicine, scientific study and identification of active plant compounds and their effects can lead to the discovery of new therapeutic benefits and the production of nature-based products in the future. To achieve this purpose, extensive research is fundamentally important to control the quality of raw drugs and the formulation to justify their use in the modern medicine system; subsequently, animal studies and clinical trials are required to use the benefits of these plants. In addition, in the development of medicine from medicinal plants, among other things, a practical plan should be developed to preserve these resources.

### Authors' contributions

ZL contributed to design of the study, supervised the research and manuscript editing, HA helped the preparation of the manuscript. FJ performed the searching, data collection and prepare manuscript drafting. All authors read and confirmed the final version of the manuscript for publication.

### Conflict of interests

The authors declare no conflict of interest.

### Ethical considerations

Ethical issues have been observed by the authors.

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