Herbal Drug Discovery: Challenges and Perspectives

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Abstract: Plants are very useful to mankind, and many plants are exclusively used by humans for medical purposes to prevent or treat diseases. In recent decades, natural products including medicinal plants have gained major attention in the pharmaceutical research field. Medicinal plants are the richest and commonly available sources for drug discovery. Many pharmaceutical lead molecules are derived from plants. The cost of the treatment, duration of illness and adverse effect/toxicity of allopathic drugs cause an increase in the use of alternative systems of medicines, which lead to the drastic development of herbal drugs industry. The estimated market for pharma and pharma products in 2022 is $1.12 trillion and this indicates the global pharma needs. This may be due to changes in lifestyle and increased risk of infection globally. The World Health Organization recommends the practice of the traditional system of medicine as it is affordable, safe and culturally acceptable. The objective of this review article is to summarize the importance of plants in drug discovery, current perspectives and challenges.

Keywords: Adulteration, drug discovery, medicinal plants, panchamahabhutas, prakriti, toxicity, tridosha.

1. INTRODUCTION

Medicinal plants are globally used as substances to prevent or treat diseases. The early documented records of herbal drugs date back to 5,000 years in China and India, indicating the importance of plants in healthcare system [1]. Fossil records date the human use of plants as medicines at least to the middle Paleolithic ages, some 60,000 years ago. According to the World Health Organization (WHO), about 80% of world population are dependent on plant-based systems of medicine for their primary healthcare needs and medicinal plants contribute 80% of the raw materials in the traditional medical system [2]. At the same time, the demand of herbal drugs and their popularity is increasing day-by-day. The side effects and toxicity of allopathic drugs cause the increase in the use of alternative systems of medicines which lead to the drastic development of herbal drug industry [3, 4]. People living in developing countries are especially using herbal drugs for the treatment of any diseases and disorders as they are considered as part of the culture in those communities [5]. Plants are gaining greater attention among researchers to discover new leads, thereby fulfilling the healthcare needs and reducing the number of deaths due to untreatable infections. The usage of herbal medicines has been constantly increasing every year, and it has been estimated that one-third of Americans use herbal products [6].

Drug discovery is a process to discover new drug candidates from natural resources or by chemical synthesis. If the compound exhibits pharmacological action with a low toxic profile in pre-clinical experiments, they will be subjected to clinical trials as new therapeutic agents [7]. Plants are richest and commonly available sources for drug discovery. Fabricant and Farnsworth identified 122 compounds with defined structure which were obtained from 94 species [8]. However, angiosperms/flowering plants are distributed in ~295,383 species, including ~308,312 species of vascular plants, and this plant species can be considered as potential sources for obtaining lead molecules/pharmaceutical agents [9]. The need of pharmaceutical substances is increasing in global population and to meet this need, researchers are searching the lead from natural resources including plants. The changes in environmental conditions may cause biodiversity to decline, and this may increase the number of vulnerable plants. More than 79,800 species are listed in the International Union for Conservation of Nature (IUCN) red
list, and more than 23,000 are under the category of “threatened with extinction” including 13% of birds, 25% of mammals, 33% of reef-building corals, 34% of conifers, and 41% of amphibians [10]. The domestic and inappropriate plant collection also interferes with the medicinal value of herbas. Hence, the current review article is aimed to summarize the problems with herbal on drug discovery, the importance of plants in drug discovery, current perspectives, challenges and personalized approaches regarding the uses of medicinal plants.

2. IMPORTANCE OF PLANTS IN DRUG DISCOVERY

Since prehistoric time, humans are using plants and other natural resources as nutritional supplements and to treat various diseases. According to fossil records, the use of plants by humans as medicine may be traced back to at least 60,000 years [11, 12]. Plants are commonly used as ingredients in various traditional medicine systems, such as Ayurveda, Kampo, Siddha, traditional Chinese medicine, traditional Korean medicine, Unani, etc. The modern usage of drugs began in the early nineteenth century by German pharmacists, Friedrich Serturner, who discovered morphine in 1804. Since the mid-1980s, approximately 60% of the drugs have been derived from natural resources. The era of synthetic drugs started with the discovery of chloral hydrate in 1869 by Justus von Liebig, a professor of chemistry in Giessen (Germany) [13, 14]. Almost 50% of all approved new drugs were based on natural products between the year 1994 and 2007. During the year 2005–2007, 13 natural product-based drugs were approved by drug agencies, which indicate the importance of plant/natural resources on drug development process [15]. Butler et al. reviewed 100 natural products and natural product-derived compounds, and 33 antibody-drug conjugates with a natural product-derived cytotoxic agent which are in clinical trials, and a number of natural products which are under cancer clinical trials [16]. The discovery of vinea alkaloids in 1950’s from the flowers of Catharanthus roseus and paclitaxel from the bark of Taxus brevifolia in 1967 lightened the importance of plants in the area of anticancer drug discovery [17, 18]. Before that, many pharmaceutical agents were obtained from natural products to prevent and treat systemic disorders.

The compounds which are in development today not only target a variety of indications, mainly cancer and infectious diseases of bacterial, viral, fungal, and parasitic origins, but also address other therapeutic areas, such as cardiovascular diseases, neurological illnesses and depression, metabolic diseases such as diabetes, cholesterol management, and inflammatory diseases. The cytotoxic properties of many secondary metabolites from marine organisms and bacteria are of particular interest for the development of new anticancer treatments. Some natural products are effective for infectious diseases because most of these compounds evolved from microbial warfare and show activity against other microorganisms at low concentrations [19].

3. CURRENT PROSPECTIVE ON HERBAL DRUG DISCOVERY

The estimated or projected market of pharma and pharma products in 2022 is $1.12 trillion and this indicates the rising global demand for pharmaceutical products [20]. The changes in lifestyle, food habits and environmental changes/pollution have increased the risk of infection and acquiring diseases among global population. To meet the healthcare needs of the global population, the WHO recommends the practice of the traditional system of medicine as it is affordable, safe and culturally acceptable [21]. In China, traditional medicine accounts for 40% of all healthcare delivered, and the use of traditional medicine meets the needs of developing countries [22]. In the recent years, many researches have been carried out with the intention to investigate and discover new drugs, or modify the existing drugs in order to improve the quality of life of human beings and subsequently the healthcare outcomes.

The current trend of drug discovery is the process in which a disease target is identified, validated and a chemical compound is developed to interact with the target [23]. Many new diseases, such as acquired immune deficiency syndrome (AIDS) and Ebola which emerged in the past few decades still do not have any validated cure. Tuberculosis has re-emerged as another threat, whereby it is resistant to chemotherapeutic agents that are available now-a-days [24]. However, the synthetic chemists have so far failed to solve these challenges. In lieu of this, the herbal drug domain could be another alternative route to solve these health challenges, as herbal drugs are less costly, widely accepted and are less toxic when compared to allopathic medicines. About 25 to 50% of the overall pharmaceutical drugs are derived from plants. Many anticancer drugs including vinblastine, irinotecan and etoposide were obtained from plant sources [25]. Herbal drugs may appear to exhibit new clinical effects as an alternative choice for the treatment of diseases. The multidisciplinary research approach provides new pharmacophores which may help to discover new targets [26].

Moreover, there are quite a number of government science departments in certain countries that are undertaking many laudable initiatives. For example, the Indian Council of Scientific and Industrial Research carried out some initiatives, such as Open Source Drug Discovery and New Millenium Indian Technology...
Leadership Initiative. The government of India has aimed to reduce the gap between private industries and public research institutes toward the collaborative drug discovery programs. Consequently, these programs have resulted in the discovery of essential formulations and lead molecules. For instance, 12 new drugs have been invented by Central Drug Research Institute (CSIR) which include a non-steroidal oral contracepti ve pill – “Centchroman”. In addition, S007-867 and S002-333 are two synthetic molecules that have been developed as potent inhibitors of platelet adhesion and aggregation induced by collagen. Thus, they may show therapeutic effects on thrombotic cerebral stroke and coronary artery disease [27].

Currently, the WHO has urged countries to allocate financial support for traditional practitioners to develop traditional medical systems. It is necessary to utilize both traditional and Western medical systems in order to fulfill the primary health care needs [28]. For example, *Ammi visnaga* is used to treat angina pectoris effect ively. *Cymbopogon proximus* is used for removal of urinary tract stones, and the root of Combretum is used to kill guinea-worm. *Bitter leaf* (Nigerian plant) is able to kill mouth bacteria [29, 30].

In the other perspective, there is a lack of complete information of most of the herbal drugs due to poor documentation about their composition. More research should be conducted in order to facilitate more efficient documentation of the herbal drugs and explore their medical uses so that the quality and safety issues will not be considered unauthenticated or unverified. The explanatory and pragmatic studies are meant to be complementary and useful to acquire reliable data for both patients and healthcare personnel.

At present, there is no standard practice available to determine the plant species used in the herbal products, which may lead to fraudulent and unethical practices [31]. In 2007, WHO released the “Guidelines for assessing the quality of herbal medicines with reference to contaminants and residues” to assess the quality of herbal medicines and to check for the presence of residual substances [32]. In India, the Ministry of AYUSH has taken measures to stop the unethical practices, and Ayurvedic Pharmacopoeia of India has standardized the protocol for the use of herbal materials [33].

4. ADVANTAGES OF HERBAL DRUG DISCOVERY

Herbal drugs started gaining popularity due to increase in the cost of allopathic drugs and prescriptions, and an interest in natural therapies. Thus, physicians are trying to gain knowledge on herbal drugs so that they are able to answer the questions from patients [34]. Therefore, a relationship should be established between allopathic physicians and naturopathic physicians, which will mutually help the patient as well as physicians. However, there are some advantages and disadvantages of using herbal drugs. It is better to seek the advice from naturopathic physicians or qualified herbalists to analyze the pros and cons of treatment with herbal drugs.

In the last century, developments in synthetic drugs have revolutionized the health care system and at the same time the number of adverse events are also increasing due to medication which is one of the leading causes of mortality. In Africa, up to 90% and in India upto 70% of the population depends on traditional medicine. In China, 90% of general hospitals have units for traditional medicine and they are having a long history of using herbs as a therapeutic agent. In the United States, 38% adult and 12% Childers use traditional medicine. The most common reasons for using traditional medicines are affordability, close correspondence to the patient’s ideology and allays concerns about the adverse effects of synthetic drugs [35].

Most of the herbal drugs have lesser unintended side effects as compared to pharmaceutical drugs, and thus they are considered safer to be used than the pharmaceutical drugs. Herbal drugs are cost-effective than other pharmaceutical drugs. Herbal drugs are relatively cheap as compared to allopathic drugs as they are more affordable and economical.

Natural resources have more structural diversity and novelty compared to synthetic compounds. Plant-derived drug products generally have higher molecular weights, incorporate more oxygen atoms and are more complex with more bridgehead tetrahedral carbon atoms, rings, and chiral centers. This complexity allows diverse specific binding to targets. Furthermore, the exploration of structural chemical databases comprising a wide variety of chemotypes on target genes and proteins facilitates the creation of new chemical entities through computational molecular modeling for pharmacological evaluation [36].

These advantages of plant-derived drugs can serve as the rationale for using them as good lead compounds on further modification for the drug development. The large proportion of natural products in drug discovery has stemmed from the diverse structures and the intricate carbon skeletons of natural products. The secondary metabolites from natural sources show more biological friendliness than totally synthetic molecules [37].

5. DISADVANTAGES OF HERBAL DRUG DISCOVERY

Herbal drugs are not without disadvantages and are not applicable to all situations. Although the advan-
tages are numerous, yet there are few risks associated with herbal drugs. Despite advances in technology and understanding of biological systems, drug discovery is still a lengthy, expensive, difficult, and inefficient process with low rate of new therapeutic discovery [38].

The main disadvantages are the regulations of herbal drugs. The Food and Drug Administration (FDA) of the United States has more stringent rules for the manufacturers of pharmaceutical drugs than herbal manufacturers. Pharmaceutical manufacturers need to do documentation of their products’ safety and efficacy but herbal manufacturers do not need to do those documentations before the drugs are approved and marketed to the public. Therefore, there is a risk of consumers buying inferior quality herbal medications. As the manufacturing process is not strictly regulated like pharmaceutical companies, the qualities of herbal products tend to vary from batch-to-batch, and thus the dose is hard to estimate [39].

In addition, herbal drugs also cause interactions between medications. Almost all herbal drugs have some precautions. For example, St. John’s Wort and Valerian used for anxiety can interact with antidepressant medications [40]. As with the synthetic drugs, herbal drugs also undergo drug-drug interactions and food-drug interactions, which may cause serious harmful effects. In a few of the places, patients keep changing the medication system during illness without informing the physician and are thus victimized with unexpected adverse effects.

Herbal drugs also lack dosage instructions, as most of the people take those medications by self-dosing which can lead to harmful side effects as there is a chance of accidental overdosing. Moreover, herbal drugs are ineffective for serious ailments. Some patients tend to switch their medication to herbal medications without noticing the symptoms linked to different ailments. However, in the conventional therapeutic regimen, there is a constant monitoring of patients’ health. In certain cases, non-prescription herbal drugs are taken, and might undergo trial and error, which can be harmful to them. The time to cure with herbal medication is usually longer than conventional medication. For those health conditions which need rapid relief from specific diseases, allopathic drugs may be a preferable option as compared with herbal drugs. This is because active ingredients of pharmaceutical drugs are more target specific. Some herbal drugs can also lead to allergic reactions, therefore before switching to herbal drugs, patients have to ensure that they are not allergic to the herb. The conventional medications have lower chance of allergy as they are normally taken with a prescription.

Another major disadvantage of herbal medicine is adulteration. Few of the formulations have been adulterated with steroids, and heavy metals, which may lead to renal problems. Hussin stated that, ‘37% of 3000 renal problems in Malaysia might be attributed to the chronic use of traditional herbal preparations’ and also Malaysian Ministry of health stated that almost 95% of unregistered herbal preparation contains steroids [6]. Furthermore, the shelf-life of the herbal formulation is questionable. Herbal medications slowly lose their potency from the day of collection, and it has a major impact on the formulation. The shelf-life of the purified phytoconstituents can be determined, but it is very difficult to control the quality of herbal formulation. Moreover, the herbal medicine is a mixture of chemical substances which may have differences in shelf-life and pharmacokinetics and pharmacodynamic properties, such as biological half-life, elimination half-life, drug-interactions, etc., which are major contributing factors for biological actions of a drug. This is one of the major disadvantages of herbal formulation which cannot be addressed with currently available knowledge.

6. PROBLEM WITH HERBAL DRUG DEVELOPMENT

Globally, 422,000 plant species have been identified, of which ≈ 52000 (i.e., 12.5%) plant species have been used for medical purposes and 4160 (8%) of the medicinal plants are under the ‘threatened’ category [41]. Many plants are not explored for their biological activities, and few of the plants are well identified and listed in official pharmacopoeias, such as the Japanese Pharmacopoeia and Ayurvedic pharmacopoeia of India. The 14th edition of Japanese Pharmacopoeia lists 165 herbal ingredients and the 16th edition of Japanese Pharmacopoeia lists 276 crude drugs, such as herbal medicine and extract that are approved to be used in kampo remedies [42]. The Ayurvedic Pharmacopoeia of India has the information of 976 compound formulations and 540 monographs of plants [43]. The pharmacological actions of the plants are based on their phytoconstituents and the concentration of plant phytoconstituents depends on the plant habits. The plant habit has a major impact and this factor plays a key role in medicinal importance of any plant. About 90% of the medicinal plants used in the Indian system of medicine are collected from wild and natural sources. The unsuitable collection (stage of maturity, dried haphazardly and stored for long time) is rapidly depleting the resource base and many species are under threat [44]. The following factors may be attributed to the plants for their biological activity:

1. Photosynthesis and respiration of plant: In folk medicine or traditional medicinal system, until a few decades back, the practitioner used to collect
the plants at particular seasons to achieve better therapeutic activity. However, more recently, the practitioners are cultivating the plants and collecting as needed.

2. Cultivation of medicinal plant: These days, the medicinal plants are cultivated by using modern agriculture methods. But in olden days, the medicinal plants were allowed to grow on their own, and they were collected by the practitioner for further use.

3. Environmental contamination: This is currently the major problem. The changes in environmental factors, such as sunlight intensity, rainfall, oxygen and carbon dioxide balance, nitrogen levels and soil conditions influence the plant growth, which in turn alter the medicinal value of the plants.

7. PERSONALIZED MEDICINE WITH HERBAL DRUGS

Concepts of individualized/ personalized medicine are highlighted in traditional medication system, such as Ayurveda, traditional Chinese medicine and Korean medicine [45]. Ayurveda and Siddha medicine systems believe in the concept that living microcosm (human beings) and the macrocosm (external universe) are built up with the Pancharatna in Ayurveda or the five elements, such as Vayu (air), Teja (fire), Aap (water), Prithvi (earth) and Akasha (aether). When combined in pairs, the Panchamahabhutas form three humors or Tridosha namely Vata, Pitta and Kapha. All these present the constitution or prakriti of an individual, which in turn determines the physical and mental characteristics of humans, whereas the imbalance causes diseases [46]. Different prakriti may have differences in metabolism rate. The individuals with Pitta prakriti are fast metabolizers, while those of Kapha prakriti are slow metabolizers [45]. Similarly, Ayurvedic drugs based on rasapanchaka classify the drugs based on Rasa (taste), Guna (property), Virya (potency), Vipaka (post digestive taste), and Prabhava (effect). The rasapanchaka modality provides the treatment by considering the individual’s prakriti [47].

CONCLUSION

Medicinal plants are very good sources for discovery of pharmaceutical lead molecules. Phytogeographical variations, such as changes in environmental condition, inappropriate cultivation and collection methods interfere with the biological activities of the medicinal plants. The uses of medicinal plants are based on each patient’s prakriti, and it determines the metabolic status of the users. The cultivation of medicinal plants in accordance with their habits may have rich medicinal value, and using the plant as medicine based on patient’s prakriti will reduce unexpected adverse effects.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES


