Mayuri Napagoda, D. S. A. Wijesundara

1 Medicinal plants as sources of novel therapeutics: the history, present, and future

1.1 Introduction

Plants form the basis of various traditional and folk medicines that have been in practice for thousands of years. Even today, plants are considered as a rich source of therapeutic agents for the treatment and prevention of diseases. According to the World Health Organization (WHO), approximately 80% of the inhabitants in the world depend mainly on traditional medicines for their primary health care. It is estimated that at present, more than 35,000 plant species are employed for medicinal purposes [1].

A medicinal plant is usually described as "any plant which, in one or more of its organs, contains substances that can be used for therapeutic purposes or which are precursors for the synthesis of useful drugs" [2]. These plants also become the source of natural products that can be developed into novel drugs or can be utilized as drug leads. Noteworthy, up to 50% of the approved drugs during the last 30 years are from either directly or indirectly from natural products. For example, in the area of cancer, out of the approved 175 small molecules over the time frame from the 1940s to 2014, 85 (49%) were either natural products or natural product derivatives [3]. Besides, natural dietary supplements are also gaining much popularity among the general public. Particularly, cancer patients in the USA have started to use new dietary supplements with natural ingredients after being diagnosed with cancer. These herbal medicinal products are available as single isolated/enriched compounds or as complex mixtures of several biologically active compounds. Further, these could be obtained from a single herb or combination of herbs, as polyherbal formulations and are prepared in different ways like decoction, tinctures, teas, syrups, essential oils, ointments, salves, and tablets/capsules with the powdered form of the whole plant/plant part or dried extract [4].

The increasing interest in medicinal plant research is clearly reflected by the number of recent publications that have increased more than threefold from 2008 (4,686 publications) to 2018 (14,884 publications). Fitzgerald et al. [5] revealed that the largest proportion of publications cited in current databases over the last 10 years are in the disciplines of pharmacology and pharmacy and it is followed by plant sciences, biochemical molecular biology, and agriculture research. Moreover,

Mayuri Napagoda, Department of Biochemistry, Faculty of Medicine, University of Ruhuna, 80000 Galle, Sri Lanka, e-mail: mayurinapagoda@yahoo.com
D. S. A. Wijesundara, National Institute of Fundamental Studies, 20000 Kandy, Sri Lanka

https://doi.org/10.1515/9783110595949-001

the majority of those publications have emerged from China, India, the USA, and South Korea, indicating the strong medicinal plant traditions in Asia as well as the USA's dominant presence as an international user of herbal products [5].

Thus this chapter gives a brief overview of the history of medicinal plants, the challenges faced in the development of herbal-based drugs, and some future prospects in the field of herbal medicine.

1.2 The use of medicinal plants: historical perspective

The relationship between plants and humans has been existing since time immemorial. Early humans exploited the plants around them for use as food, fuel, clothing, shelter, and medicine [6]. Fossil records indicate that prehistoric humans had used plants as medicine at least 60,000 years ago in the Middle Paleolithic age [7, 8]. It is assumed that the treatment of open wounds had included the cleaning and packing with plant parts or plant extracts, some of which might be beneficial in cleansing and healing wounds. Among the objects found with the mummified body of Ötzi the Iceman who lived about 5,300 years ago, there were woody fruits of a bracket fungus *Piptoporus betulinus*. It has been revealed that *P. betulinus* contains toxic resins and agaric acid which are powerful purgatives, along with oils that are toxic to metazoans and with antibiotic properties [9].

It is speculated that the pharmacological knowledge of primitive man might have come from experimentation and sometimes they might have judged the use and purpose of plants just by examining what the plant resembled. For example, the black speck in the flower of the plant eyebright (*Euphrasia officinalis*) appears as a pupil in the eye and thus was used for diseases in the eye. Similarly, plants with bright yellow flowers were used against jaundice in which the white parts of the eye get turned into yellowish color [10].

The oldest written evidence of the use of medicinal plants for the preparation of drugs has been found on a Sumerian cuneiform tablet which is believed to be from 3000 BC. Fifteen pharmaceutical prescriptions composed of milk, snakeskin, turtle shell, *Cassia*, myrtle, asafetida, thyme, willow, pear, fig, fir, and date have been described there, although it lacks the context on associated diseases or the amounts of the ingredients. Interestingly, all parts of plants had been used for those prescriptions. Narcotics derived from *Cannabis sativa* (hemp), *Mandragora* spp. (mandrake), *Lolium temulentum* (darnel), and *Papaver somniferum* (opium) were utilized by the ancient Mesopotamians [10, 11].

Traditional Chinese Medicine dates back to about 2500 BC and the oldest medical writings on herbs described dozens of herbs in a variety of situations related to healing and diet [12]. The Chinese book *Pen T'Sao*, written by Emperor Shen Nung

around 2500 BC, on roots and grasses revealed 365 drugs composed of dried parts of medicinal plants like yellow gentian, ginseng, cinnamon bark, camphor, *Podophyllum*, jimson weed, and *Ephedra* [13, 14].

The traditional Indian medicine, or Ayurveda, developed significantly during the Vedic period (2500–600 BC) and the descriptions of the system are available in ancient literature such as Rig-Veda, Yajur-Veda, and Atharva-Veda, which mention the utilization of plants for treatment purposes. Three groups of plants have been recognized in Rig-Veda as trees (Vriksha), herbs (Osadhi), and creepers (Virudh) while the shape and morphology of plants were also described in Atharva-Veda. Four groups of medicinal plants were described in Yajur-Veda [13, 15–17]. The Caraka-Samhita (Compendium of Maharishi Caraka) and Sushruta Samhita, dating to the period of 900–600 BC, are two fundamental texts on Indian traditional medicine and describe hundreds of pharmacologically active herbs and spices [17].

The Egyptian pharmaceutical record "Ebers Papyrus," written circa 1550 BC, is the most complete and most famous medical papyri. It describes hundreds of magical formulas and folk remedies refereeing to about 700 plant species including pomegranate, castor oil plant, garlic, onion, *Aloe*, *Senna*, fig, willow, coriander, juniper, etc. [13]. Plant extracts were prepared and either taken internally or applied topically, while some were administered by fumigation and vapor inhalation [18].

The Egyptian tradition was transmitted to Greek and Roman medical systems over time triggering the use of plant species against various ailments. Greek philosopher Aristotle (384–322 BC) has described 500 crude drugs employed in the treatment of different pathological conditions, while the Greek Physician Hippocrates (460–370 BC), the father of modern medicine, believed that disease had natural causes; thus, various herbal remedies were used in his treatments. He mentioned about 400 medicinal substances of herbal origin [15, 19].

Theophrastus (370–287 BC), who is considered as "the father of Botany," wrote two books "*De Causis Plantarium*" – Plant Etiology and "*De Historia Plantarium*" – Plant History. In these books, he included a classification of more than 500 medicinal plants known at the time [15]. Further, Theophrastus described on the season and the method for the gathering of useful medicinals; for example, the best juices are collected in the summer, while spring or autumn would be the best time to gather the most useful roots [20].

The Roman writer Cornelius Celsus (25 BC–50 AD), who wrote the book *De Medicina*, described the preparation of numerous ancient medicinal remedies and quoted about 250 medicinal plants such as *Aloe*, poppy, pepper, cinnamon, the star gentian, and cardamom [13]. In around 60 AD, the Greek physician Pedanius Dioscorides (40–90 AD) documented over 600 curative plants in his book *De materia medica* which formed the core of the European pharmacopeia. Chamomile, garlic, onion, ivy, nettle, sage, coriander, parsley, willow, etc. are some of the most appreciated domestic plants described by Dioscorides. The descriptions of the medicinal plants included their outward appearance, locality, mode of collection, preparatory

methods, and the therapeutic effects [13]. Similarly, Pliny the Elder (23–79 AD) introduced *Naturalis Historia*, a work that includes myths and folklore, trees, and medicinal plants [21].

Claudius Galen (129–199 AD) introduced the concept of pharmaceutical formulation to formulate stable and therapeutically effective drugs and published at least 30 books on plants [15, 22]. He also introduced several new plant drugs that had not been described by Dioscorides, for example, Uvae ursi folium, which had been used as an uroantiseptic and a mild diuretic [13].

During the Middle Ages, the monasteries preserved medical knowledge in Europe where monks who were in their monasteries planted and experimented on the species described in classic texts. Meanwhile, the Arabic scholars translated many classical Greek texts into Arabic and complemented it with their own medicinal expertise, as well as the knowledge of herbs from Chinese and Indian traditional medicines [23]. The Persian pharmacist and the physician Avicenna wrote "Canon Medicinae" and "Kitab Ash-Shifa," while Ibn al-Baitar recorded hundreds of medicinal plants in his "Corpus of Simples" [15, 21, 22]. Moreover, the toxic aspects of various plants were also described by Arabs, for example, *The Book on Poisons and Antidotes* by Abu Musa Jabir ben Hayyan [24].

"The Black Death," which is considered as one of the most devastating pandemics in human history, had swept through Europe in the thirteenth and fourteenth centuries. As the physicians were not knowledgeable at that time to deal with the infection, superstitious practices like burning aromatic herbs and bathing in rosewater or vinegar were also performed [21].

Although the emphasis paid on herbal sciences had declined during the late Middle Ages, several herbalists fostered this field, especially during the sixteenth century. In the dawn of Renaissance, Paracelsus (1493–1541 AD) reintroduced opium for medical use in Western Europe [25]. There was no concept of the geographical distribution of plants in the early sixteenth century, and Leonhart Fuchs (1501–1566 AD) became the first herbalist to describe the American introduction of previously unknown plants into Europe. His book *De historia stirpium* covers 497 native European and introduced plants and over 500 woodcut illustrations [26]. His work became a masterpiece and considered as the standard scholarly study on plants until Carolus Linnaeus (1707–1788 AD) introduced the new taxonomy, the binomial system [27]. Meanwhile, in England, John Gerard (1545–1612 AD) published *Herball* or *Generall Historie of Plantes*, and in 1618, London Pharmacopoeia was compiled using previous work on the medicinal plants [22].

Until the nineteenth century, medicinal plants were employed on an empirical basis, neither with mechanistic knowledge on their pharmacological activities nor with the active constituents [23]. The early nineteenth century was a turning point in the field of herbal medicine as attempts were made for the isolation of the active principles of commonly used plants such as poppy, belladonna, autumn crocus, and Saint-Ignatius' bean. These isolations were then followed by the commercialization

of morphine, the first commercial pure natural product in 1826; the aspirin, the first semi-synthetic pure drug based on a natural product in 1899; and many other pharmaceutically important natural products thereafter [22].

Despite the advent of other drug discovery approaches like molecular modeling and combinatorial chemistry, the impact of natural products as new clinical candidates in the drug discovery programs is still very high. For example, 1,073 new chemical entities belonging to the group of small molecules had been approved between the period of 1981 and 2010 and more than half of those were based on natural product scaffolds. Interestingly, a substantial number of these compounds were from higher plants [23]. Thus natural-product-derived compounds are still proving to be an invaluable source of medicines for humans and the indigenous knowledge on medicinal plants play a vital role in expanding the horizons of the modern pharmaceutical industry. In this respect, ethnobotanical studies could be indispensable tools for gathering folklore knowledge.

1.3 Ethnobotany in drug discovery: pros and cons

The term "ethnobotany" was first introduced in 1896 as "the study of plant use by humans" by an American botanist John Harshberger. Thus it studies various aspects of how plants are used by people as food, cosmetics, textiles, and medicines including all the beliefs and cultural practices associated with their use [28]. On the other hand, the more recently introduced term "ethnopharmacology" describes a multidisciplinary area of research, concerned with the observation, description, and experimental investigation of indigenous drugs and their biological activities [29]. Ethnobotany has undergone a radical transformation during the last two decades [30].

Leopold Glück, a German physician working in Sarajevo, published his work on traditional medical uses of plants among the rural people in Bosnia in 1896, and it is believed that this work would be the first modern ethnobotanical work [31]. Since then a large number of ethnobotanical studies were carried out in different regions around the globe and some of the notable work includes those of Richard Evans Schultes and his students such as Wade Davis and Mark Plotkin in the South American Amazon [32].

Ethnobotanical studies play an important role in the preservation of traditional knowledge through proper documentation. A study of a rural population in Argentina revealed that for the transmission of knowledge of medicinal and edible plants, family members (especially mothers) play a major role while experienced traditional healers outside the family also made a great contribution [33, 34]. As smaller and more vulnerable tribes and indigenous groups become increasingly fragmented and threatened by modern development pressures in developing countries, it is feared that folk knowledge might get lost forever [34]. Also in some communities, the wealth of knowledge

is rapidly diminishing not only due to the dearth of elderly people who are knowledgeable on traditional healing systems but also due to the lack of interest in the younger generation to acquire this knowledge systematically [35]. Also, dramatic destruction of ecosystems and the ruthless use and overexploitation of medicinal plants solely for commercial purposes compel to accelerate studies of ethnomedicine along with biomedical and phytochemical studies for the development of new natural products and drugs needed by humans [34, 35].

Ethnobotanical studies are proven to be an effective approach to reveal the hidden potential of plants against various illnesses and thereby could contribute toward the drug discovery programs by providing information on the selection of plants or specific phytochemicals to be tested in experimental models of various diseases. On several occasions, the results of ethno-directed investigations have been compared with random search for plants for specific therapeutic purposes. According to Khafagi [36], 83% of the plants in Sinai, Egypt selected using an ethnobotanical approach elicited antimicrobial activities while only 42% of the randomly selected plants exhibited the bioactivity [36]. Similarly, Slish et al. [37] reported that 4 out of 31 plants selected in Belize using the ethno-directed study displayed vascular smooth muscle relaxant activity; however, none of the randomly collected 32 plants exhibited this property [37].

However, there are number of pitfalls associated with ethnobotanical/ethnopharmacological studies, particularly concerning the design of studies and collection and interpretation of data. This demands proper training and sound knowledge of the international literature from investigators of theoretical and methodological contributions to this field. Besides, the selection of plants relevant for bioprospecting based on their popularity and usefulness is sometimes doubtful, while the exclusion of information essential for efficiently testing the plants is another error observed in the latest ethnobotanical studies. In order to overcome these limitations, it is recommended that researchers should clearly establish the goals of their study, for example, whether they are going to study one single and well-defined therapeutic activity, or the full range of knowledge of the local medical system. Further, during the selection of informants for the study, the age, gender, and social function of the individuals should be considered, particularly the role of women and elders who are supposed to possess greater knowledge on medicinal plants due to their role in the home and family care, and their longer interaction with the environment respectively. Also, the researchers should keep in mind that the high presence and importance of a particular plant in a local healing system might not always be linked to its pharmacological effect, whereas plants that are mentioned less frequently might be important for bioprospecting; thus, low popularity does not necessarily mean lack of efficacy. Because of the cultural validation and the local belief in its effectiveness, a widely popular plant may act like a "placebo," despite the absence of biologically active compounds. Moreover, the plant species located geographically closer to a local community may be used more often, thus imparting greater importance. On the other hand, a plant that has been rarely

mentioned could be a recent introduction to a local medical system, or else, the knowledge on its healing potential might have been restricted to a few families or individuals as a family secret or has a low availability in the study area concerned. Therefore, such rarely mentioned plants might actually be highly valuable from the bioprospecting perspectives [38].

Although the "ethnobotanical approach to bioprospecting" has resulted in the development of at least 88 new pharmaceuticals like the muscle relaxant tubocurarine and the antimalarial drug quinine, there were instances where this approach was not as effective as it was anticipated. A well-known example was the project conducted by Shaman Pharmaceuticals in South San Francisco, California, USA, with the vision "collaborating with the rainforest's indigenous people as part of a sophisticated drug discovery and development process of modern Western medicine" [39]. A team of botanists and physicians were sent to 30 countries to work directly with indigenous communities and to interview the traditional healers to learn about the plants that are used to treat illnesses and how the patients are treated. Although the initial interest was directed toward antifungal and antiviral agents, the active compounds discovered were failed in the clinical trials; thus, the efforts were made to assess the antidiarrheal activity. "SP-303," a mixture of proanthocyanidin polymers isolated from the latex of *Croton lechleri* was found to be clinically efficacious and developed as a dietary supplement for diarrhea. It has been realized that the applications were different from indigenous ethnobotanical uses of *Croton* sap. Despite the collection of 1,000 plants and screening of 800, of which 420 identified with biological activity and leading to 20 patents, the Shaman project is considered as a victim of bad timing in its choice of the search strategy. The failure of the project signifies the need for new models of these approaches to drug development as well [7, 39].

The researchers involved in the collection of ethnobotanical knowledge of indigenous people should be aware of Convention on Biological Diversity (CBD) and intellectual property rights; thus, it is recommended to obtain prior informed consent for the use of the resources of those indigenous people and their traditional knowledge. Gaining the consent of indigenous people is a time-consuming process that involves the identification of appropriate indigenous communities to work with and getting their approval for sharing knowledge and resources as well as negotiation of appropriate contracts and compensation packages [39, 40].

Because of the complicated issues associated with ethnobotanical research, pharmaceutical companies prefer to use literature and database search rather than conducting ethnobotanically directed search itself [39]. NAPRALERT is one of the famous databases that were designed to evaluate the literature on natural products for the identification of new sources of commercially significant or clinically useful drugs. This database contains data on upward of 60 000 species, including more than 200,000 distinct chemical compounds of natural origin and 90,000 reports of ethnomedical uses of plants as well as other organisms. More than 770,000 unique

pharmacological records are there representing more than 4,000 different pharmacological activities. These data have been extracted from over 200,000 scientific articles and reviews from approximately 10,000 scientific journals. Thereby it provides essential information to researchers who are engaged in medicinal plant research and drug development as well as the botanical dietary supplement industry [41].

There are several other herbal medicine databases with scientific data on the use and study of herbs for health, namely, the herb information knowledgebase (THINKherb) database, Traditional Chinese medicine information database (TCM-ID), Traditional Chinese medicine integrated database (TCMID), and Indian Plant Anticancer Compounds Database (InPACdb). THINKherb contains 499 herbs, 1,238 genes involving human, mouse, and rat, 825 diseases, 245 pharmacological activity, and 373 signaling pathways. TCM-ID composed of 1,588 prescriptions, 1,313 herbs as well as 5,669 herbal ingredients along with the 3D structure of 3,725 herbal ingredients. TCMID contains 47,000 prescriptions, 8,159 herbs, 25,210 compounds, 6,828 drugs, 3,791 diseases, and 17,521 related targets. On the other hand, InPACdb provides comprehensive information on anticancer activity of the phytochemicals of Indian origin. As of recent times, these databases turned out to be a valuable resource for drug development and drawn the attention of researchers in both academia and industry [1].

1.4 From plants to the pharmacy shelf: the drug development process

The development of new drugs from the plant sources is a complex, time-consuming, and expensive process (Figure 1.1) as it is carried out in three elaborate steps, namely, pre-drug stage, quasi drug stage, and full drug stage. The first stage of drug development is the pre-drug stage and involves the information-driven selection of plants either based on indigenous use or from the results obtained in animal studies. Then in the quasi drug stage, the extracts are prepared, phytochemicals are screened, and the structure and composition are elucidated. Further, the bioactivity evaluations are conducted for the identification of possible lead compounds. If necessary, the lead compounds are subjected to structural modifications as well. Once the lead compound is identified, it is structurally modified if needed. Thereafter, it is evaluated in animal models, *in vitro* studies, and clinical trials, and upon the approval, it enters as a marketed drug [4].

The new drug candidate (irrespective of whether a phytochemical or not) must undergo pre-clinical trials followed by different stages of clinical trials, i.e., Phase 0 (optional), Phase I, Phase II, Phase III, and Phase IV. Preclinical studies are required before the initiation of the clinical trial. These pre-clinical studies involve *in vitro* and animal experiments (*in vivo*) at different doses of the study drug to determine the pharmacodynamics, pharmacokinetics, and toxicology of the drug.

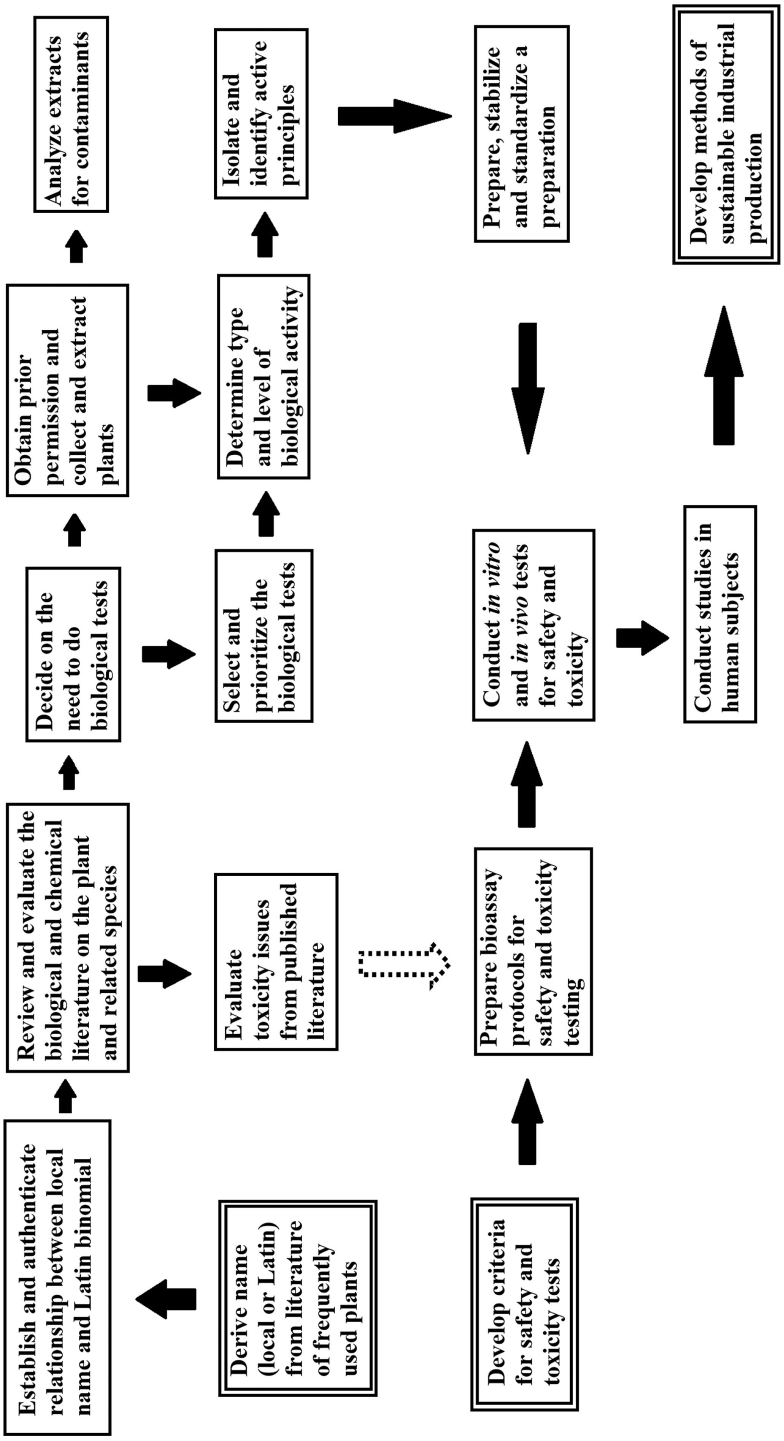

Figure 1.1: A flow chart for the study of plants used in traditional medicine (adapted from Cordell and Colvard, 2005 [40]).

Phase 0 experiments are optional exploratory trials where a small group of individuals, usually 10–15, are tested with a single, sub-therapeutic dose to gather pharmacokinetic information, thus to access whether the drug candidate performs as expected to take forward into further development. Then in Phase I studies, the new drug is administered to 20–100 normal healthy individuals to determine the maximum tolerated dose of the drug, the common and serious adverse effects of the drug, and also its pharmacological, pharmacodynamic, and pharmacokinetic properties. Nearly 70% of drug candidates move from Phase I to Phase II. Phase II studies are conducted with several hundred patients with specific diseases. The study population is well defined by inclusion and exclusion criteria, and based on the dose or dose range determined in Phase I, dose-response in patients and the drug's biological activity and efficacy are evaluated. Approximately one-third of tested new drugs move into Phase III trials which are carried out using a large number of patients and with specific diseases to determine efficacy, effectiveness, and long-term side effects. Usually, about 25% to 30% of the new drug candidates progress to the next phase, Phase IV. Phase IV trials are long-term studies involving more than 10,000 individuals of the relevant patient population and normally conducted after the approval of the regulatory agency. This study aims to assess the drug's real-world effectiveness. In some instances, the outcome of Phase IV studies could lead to a withdrawal of the drug from the market or for a restriction to particular uses [42].

Despite the fact that many botanicals are in the pipeline of clinical trials, only a few have ended up as a commercial drug, hence the rest failed at different stages of the clinical trial. One example is a different formulation of "SP-303" identified in the project undertaken by Shaman Pharmaceuticals. This formulation called "Virend" was developed as a topical formulation for the treatment of genital herpes, and it progressed to the clinical trials from the pre-clinical stage within a short period, i.e., after 24 months of laboratory testing. However, Shaman Pharmaceuticals halted the further development of Virend when it demonstrated no additional benefit over the existing drug for herpes, acyclovir [39]. Similarly, several natural dietary supplements have undergone Phase II trials of cancer therapy; however, the majority failed to progress to Phase III trials, in spite of their positive results in pre-clinical investigations with animal models, cell lines, and/or small early phase clinical trials [4].

There are many challenges encountered in the development of herbal drugs. For example, randomized, placebo-controlled trials are crucial in the evaluation of any drug for health benefits or disease mitigation; however, the peculiar color, taste, and smell in herbal medicine make it difficult to conduct placebo-controlled trials. There were many occasions where the clinical evaluation of herbal drugs had shortcomings in trial design, improper execution, and weak data analysis, particularly due to the inappropriate number of patients in trials, improper randomization, and selection bias. Also conducting pharmacokinetic studies on polychemical natural products is quite complicated unless the active ingredient/active principle is known. The presence of several different active ingredients makes the pharmacokinetic evaluation

more difficult and complex. Poor standardization and lack of quality control of herbal preparations as well as the presence of several active compounds would make the dose calculation a tedious process and sometimes lead to discrepancies in the dosage and treatment duration of the herbal remedies. Moreover, the contamination or adulterations of herbal preparations might result in undesirable toxic effects sometimes with dire consequences [4].

1.5 Conservation of medicinal plants

The use of herbal drugs shows an increasing global trend and the wild populations of plants having medicinal properties are facing many threats as a result. Therefore, the need for conservation of those plants has now become a priority [30, 43]. According to Heywood [30], this poses several problems. The numbers of medicinal plant species involved are large and information on the conservation status of the majority of the species are lacking. Threats faced by over-collecting, insufficient knowledge on the genetic variation and indigenous traditional knowledge are other problems. The reluctance of the policy makers to become involved and invest in conservation of these species is another critical issue.

1.6 The future trends in the medicinal plant research

Despite the numerous deterrents in the field of phytomedicine, researchers all over the world are conducting pre-clinical studies and clinical trials with botanicals to harness the maximum benefits from the healing powers of plants. Moreover, agencies like the National Institute of Health, USA; European Medicines Agency (EMA); Indian Council of Medical Research; and National Health and Medical Research Council, Australia, are undertaking clinical trials in assistance with several governments and private institutes [4].

The application of metabolomics in natural products research is a recent trend that is aimed at the qualitative and quantitative analysis of all the metabolites of an organism at a specific time and under specific conditions. Analytical techniques like high-resolution mass spectrometry and nuclear magnetic resonance spectroscopy are employed here to dereplicate and quantify the known metabolites against novel natural products. Along with metabolomics-guided fractionation tools, it is possible to identify active components at the first fractionation step, as well as to predict the metabolites that might be bioactive. Further, the metabolomics approach could help in

the prioritization of fractions for further purification, saving time, and resources in isolating the target compounds [44].

With the progress in bioinformatics, computational techniques have entered in the process of drug discovery and development, and often precede or complement *in vitro* and *in vivo* studies. These computer-aided or *in silico* design is being utilized to expedite and facilitate hit identification, hit-to-lead selection, optimize the absorption, distribution, metabolism, excretion, and toxicity profile and avoid safety issues [45, 46]. These integrated computer-assisted strategies would be beneficial in processing a large amount of available structural and biological information within a short period of time for a straight-forward search of bioactive natural products [47].

Although there are significant numbers of very potent phytochemical compounds particularly with anti-tumor activity, the nonspecific administration (i.e. dosing the whole animal) during testing would lead to very high toxicities. The delivery of such agents specifically to the tumor area would enable to use those materials for treatment. In this respect, liposome-encapsulated toxic agents and antibody-conjugates with natural toxins/pure compounds would be an ideal strategy [22]. Moreover, the low bioavailability of phytochemicals would also hamper the further development of these agents. The use of nanoparticles is one of the promising strategies to significantly increase the bioavailability of natural products. The improvement in their pharmacokinetic properties might lead to a better therapeutic effect, without high-dose-induced acute toxicity. In this respect, polymeric nanoparticles have been employed to increase the bioavailability of luteolin, epigallocatechin gallate (EGCG), tea polyphenols, and silibinin while the oral bioavailability of apigenin was improved by incorporating it into a carbon nanopowder solid distribution [48]. Moreover, an improvement in the molecular targeting, oral bioavailability, and anticancer efficacy was observed for the new ginsenoside, 25-OCH3-PPD (GS25) isolated from *Panax notoginseng* upon its encapsulation into PEG-PLGA nanoparticles [49]. These examples indicate that the role of nanotechnology would be imperative to the field of herbal medicine in the coming years.

1.7 Conclusion

The plant-based healing systems continue to play an essential role in health care while functioning as an important source of novel pharmacologically active compounds. Despite the availability of compounds derived from computational and combinatorial chemistry as new drug leads as well as the challenges confronted over the years during the development of herbal-based drugs, phytochemicals still hold a fair share in drug discovery programs owing to their incomparable chemical diversity and novel mechanisms of action.

References

[1] Pan SY, Zhou SF, Gao SH, Yu ZL, Zhang SF, Tang MK, Sun JN, Ma DL, Han YF, Fong WF, Ko KM. New Perspectives on how to discover drugs from herbal medicines: CAM's outstanding contribution to modern therapeutics. Evid Based Complementary Altern Med 2013, 2013 Article ID 627375, 25 pages 10.1155/2013/627375.

[2] Sofowora A, Ogunbodede E, Onayade A. The role and place of medicinal plants in the strategies for disease prevention. Afr J Tradit Complement Altern Med 2013, 10(5), 210–229.

[3] Newman DJ, Cragg GM. Natural products as sources of new drugs from 1981 to 2014. J Nat Prod 2016, 79(3), 629–661.

[4] Chugh NA, Bali S, Koul A. Integration of botanicals in contemporary medicine: Road blocks, checkpoints and go-ahead signals. Integr Med Res 2018, 7(2), 109–125.

[5] Fitzgerald M, Heinrich M, Booker A. Medicinal plant analysis: A historical and regional discussion of emergent complex techniques. Front Pharmacol 2020, 10, 1480. 10.3389/fphar.2019.01480.

[6] Jamshidi-Kia F, Lorigooini Z, Amini-Khoei H. Medicinal plants: Past history and future perspective. J Herbmed Pharmacol 2018, 7(1), 1–7.

[7] Fabricant DS, Farnsworth NR. The value of plants used in traditional medicine for drug discovery. Environ Health Perspect 2001, 109(Suppl 1), 69–75.

[8] Yuan H, Ma Q, Ye L, Piao G. The Traditional Medicine and Modern Medicine from Natural Products. Molecules 2016, 21, 559. 10.3390/molecules21050559.

[9] Capasso L. 5300 years ago, the Ice Man used natural laxatives and antibiotics.Lancet 1998, 352(9143), 1864. 10.1016/S0140-6736(05)79939-6.

[10] Kelly K. the history of medicine early civilizations: Prehistoric times to 500 C.E. facts on file. NY, USA, 2009.

[11] Teall EK. Medicine and doctoring in ancient Mesopotamia. GVJH 2014, 3(1), Article 2 https://scholarworks.gvsu.edu/gvjh/vol3/iss1/2 Accessed on 10. 01.2020.

[12] Gu S, Pei J. Innovating Chinese herbal medicine: From Traditional health practice to scientific drug discovery.Front Pharmacol 2017, 16(8), 381. 10.3389/fphar.2017.00381.

[13] Petrovska BB. Historical review of medicinal plants' usage. Pharmacogn Rev 2012, 6(11), 1–5.

[14] Sewell RDE, Rafieian-Kopaei M. The history and ups and downs of herbal medicine usage. J HerbMed Pharmacol 2014, 3(1), 1–3.

[15] Khan H. Medicinal plants in light of history: Recognized therapeutic modality. J Evid Based Complementary Altern Med 2014, 19(3), 216–219.

[16] Kumar S, Dobos GJ, Rampp T. The significance of Ayurvedic medicinal plants. J Evid Based Complementary Altern Med 2017, 22(3), 494–501.

[17] Balkrishna A, Mishra RK, Srivastava A, Joshi B, Marde R, Prajapati UB. Ancient Indian rishi's (Sages) knowledge of botany and medicinal plants since Vedic period was much older than the period of Theophrastus, A case study- who was the actual father of botany?. Int J Unani Integ Med 2019, 3(3), 40–44.

[18] Halberstein RA. Medicinal plants: Historical and cross-cultural usage patterns. Ann Epidemiol 2005, 15(9), 686–699.

[19] Solomou AD, Martinos K, Skoufogianni E, Danalatos NG. Medicinal and aromatic plants diversity in Greece and their future prospects: A review. Agric Sci 2016, 4(1), 9–21.

[20] Scarborough J. Theophrastus on herbals and herbal remedies. J Hist Biol 1978, 11(2), 353–385.

[21] Hajar R. The air of history (Part II) medicine in the Middle Ages. Heart Views 2012, 13, 158–162.

[22] Newman DJ, Cragg GM, Snader KM. The influence of natural products upon drug discovery (Antiquity to late 1999). Nat Prod Rep 2000, 17(3), 215–234.
[23] Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, Linder T, Wawrosch C, Uhrin P, Temml V, Wang L, Schwaiger S, Heiss EH, Rollinger JM, Schuster D, Breuss JM, Bochkov V, Mihovilovic MD, Kopp B, Bauer R, Dirsch VM, Stuppner H. Discovery and resupply of pharmacologically active plant-derived natural products: A review. Biotechnol Adv 2015, 33(8), 1582–1614.
[24] Saad B, Azaizeh H, Abu-Hijleh G, Said O. Safety of traditional Arab herbal medicine. Evid Based Complement Alternat Med 2006, 3(4), 433–439.
[25] Duarte DF. Opium and opioids: A brief history. Rev Bras Anestesiol 2005, 55(1), 135–146.
[26] Elliott B. The world of the Renaissance herbal. Renaissance Studies 2011, 25(1), 24–41.
[27] Classen A, Meyer FG, Trueblood EE, Heller JL. The Great Herbal of Leonhart Fuchs. De historia stirpium commentarii insignes.Ger Stud Rev 2001, 24(3), 595–597. 10.2307/1433419.
[28] Ghorbani A, Naghibi F, Mosaddegh M. Ethnobotany, ethnopharmacology and drug discovery. Iran J Pharm Sci 2006, 2(2), 109–118.
[29] Soejarto DD, Fong HHS, Tan GT, Zhang HJ, Ma CY, Franzblau SG, Gyllenhaal C, Riley MC, Kadushin MR, Pezzuto JM, Xuan LT, Hiep NT, Hung NV, Vu BM, Loc PK, Dac LX, Binh LT, Chien NQ, Hai NV, Bich TQ, Cuong NM, Southavong B, Sydara K, Bouamanivong S, Ly HM, Van Thuy T, Rose WC, Dietzman GR. Ethnobotany/ethnopharmacology and mass bioprospecting: Issues on intellectual property and benefit-sharing. J Ethnopharmacol 2005, 100(1–2), 15–22.
[30] Heywood VH. Biodiversity, conservation and ethnopharmacology. In: Heinrich M, Jaeger A eds. Ethnopharmacology. 1st Oxford, UK, John Wiley & Sons, 2015, 41–51.
[31] Pieroni A, Quave CL. Ethnobotany and biocultural diversities in the Balkans: Perspectives on sustainable rural development and reconciliation. NY, USA, Springer Science, 2014.
[32] Nolan JM, Turner NJ. Ethnobotany: The study of people-plant relationships in ethnobiology. In: Anderson EN, Pearsall D, Hunn E, Turner N eds. Ethnobiology. 1st NJ, USA, John Wiley & Sons, 2011, 133–145.
[33] Lozada M, Ladio AH, Weigandt M. Cultural transmission of ethnobotanical knowledge in a rural community of Northwestern Patagonia, Argentina. Econ Bot 2006, 60, 374–385.
[34] Reyes-García V. The relevance of traditional knowledge systems for ethnopharmacological research: Theoretical and methodological contributions. J Ethnobiol Ethnomed 2010, 6, 32. 10.1186/1746-4269-6-32.
[35] Napagoda MT, Sundarapperuma T, Fonseka D, Amarasiri S, Gunaratna P. Traditional uses of medicinal plants in Polonnaruwa district in North Central Province of Sri Lanka. Scientifica 2019, 2019, 9737302. 10.1155/2019/9737302.
[36] Khafagi IK, Dewedar A. The efficiency of random versus ethno-directed research in the evaluation of Sinai medicinal plants for bioactive compounds. J Ethnopharmacol 2000, 71, 365–376.
[37] Slish DF, Ueda H, Arvigo R, Balick MJ. Ethnobotany in the search for vasoactive herbal medicines. J Ethnopharmacol 1999, 66, 159–165.
[38] Albuquerque UP, Medeiros PMD, Ramos MA, Ferreira J, Washington S, Nascimento ALB, Avilez WMT, Melo JGD. 2014. Are ethnopharmacological surveys useful for the discovery and development of drugs from medicinal plants?. Rev Bras Farmacogn 2014, 24(2), 110–115.
[39] Clapp RA, Crook C. Drowning in the magic well: Shaman pharmaceuticals and the elusive value of traditional knowledge. J Environ Dev 2002, 11(1), 79–102.
[40] Cordell GA, Colvard MD. Some thoughts on the future of ethnopharmacology. J Ethnopharmacol 2005, 100(1–2), 5–14.
[41] Graham JG, Farnsworth NR. The NAPRALERT database as an aid for discovery of novel bioactive compounds. In: Mander L, Liu HW, eds, Comprehensive natural products II. 1st, Amsterdam, The Netherlands, Elsevier Science, 2010, 81–94.

[42] Honek J. Preclinical research in drug development. Medical Writ 2017, 26(4), 6–8.
[43] Randriamiharisoa M, Kuhlman AR, Jeannoda V, Rabarison H, Rakotoarivelo N, Randrianarivony T, Raktoarivony F, Randrianasolo A, Bussmann RW. Medicinal plants sold in the markets of Antananarivo, Madagascar. J Ethnobiol Ethnomed 2015, 11, 60. 10.1186/s13002-015-0046-y.
[44] Harvey AL, Edrada-Ebel R, Quinn RJ. The re-emergence of natural products for drug discovery in the genomics era. Nat Rev Drug Discov 2015, 14(2), 111–129.
[45] Harvey AL. Natural products in drug discovery. Drug Discov Today 2008, 13(19–20), 894–901.
[46] Kapetanovic IM. Computer-aided drug discovery and development (CADDD): In silico-chemico-biological approach. Chem Biol Interact 2008, 171(2), 165–176.
[47] Rollinger J, Langer T, Stuppner H. Integrated in silico tools for exploiting the natural products' bioactivity. Planta Med 2006, 72(8), 671–678.
[48] Watkins R, Wu L, Zhang C, Davis RM, Xu B. Natural product-based nanomedicine: Recent advances and issues. Int J Nanomedicine 2015, 10, 6055–6074.
[49] Voruganti S, Qin JJ, Sarkar S, Nag S, Walbi IA, Wang S, Zhao Y, Wang W, Zhang R. Oral nano-delivery of anticancer ginsenoside 25-OCH3-PPD, a natural inhibitor of the MDM2 oncogene: Nanoparticle preparation, characterization, *in vitro* and *in vivo* anti-prostate cancer activity, and mechanisms of action. Oncotarget 2015, 6(25), 21379–21394.