Herbal Medicines as a Rational Alternative for Treatment of Human Diseases

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Abstract

Herbal medicines (HMs) are receiving considerable attention as the complementary drugs throughout the world due to their cost effectiveness, low toxicity, and therapeutic potential against wide range of human illness. These plants possess a wide range of bioactive principles which alone or synergistically act on different targets. Even in the modern era of medicine and technology, more than 80% of the modern medicines currently available and one-third population of the developing countries largely depend on plant products either directly or indirectly for their primary health care. Several plants such as *Aegle marmelos*, *Atropa belladonna*, *Azadirachta indica*, *Catharanthus roseus*, *Camptotheca acuminata*, *Colchicum autumnale*, *Curcuma longa*, *Digitalis lanata*, *Eclipta alba*, *Ocimum sanctum*, *Papaver somniferum*, *Phyllanthus emblica*, *Rauvolfia serpentina*, *Taxus brevifolia*, and several other high value plants have been well acknowledged for its pharmacological importance to treat important human diseases like diabetes, cancer, dementia, epilepsy, hepatitis, fever, kidney stone, malaria, mouth ulcer, and other important disorders in indigenous system of medicine. In spite of their great potential against different human diseases, the HMs have faced several acceptance issues for the practical application due to lack of scientific and clinical evidence regarding their biochemical mode of action on particular cells, tissues, or organs. Therefore, a mass-scale clinical trials and specific documentation on its molecular mode of action is needed. Based on the aforementioned background, the present chapter describes the documentation of important medicinal plants and their derived bioactive principles, potential to combat important human diseases with underlying mode of action to facilitate

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direction for reproducible drug discovery, which are safe, cost effective, and rational alternatives to the modern remedies.

Keywords

Herbal medicine · Mode of action · Pharmacological properties · Drug discovery · Bioactive principles

Abbreviations

CVDs	Cardiovascular diseases
HMs	Herbal medicines
TCMs	Traditional Chinese medicines
SCM	Sasang constitutional medicines
ROS	Reactive oxygen species
HIV	Human immunodeficiency virus
AIDS	Acquired immune deficiency syndrome
EOs	Essential oils
CAM	Complementary and alternative medicine
IPR	Intellectual property right

2.1 Introduction

Since last few decades, people throughout the world and especially in developing countries have faced several challenges associated with health care. Many diseases like diabetes, tuberculosis, epilepsy, asthma, Alzheimer's, cancers, Parkinson's, cardiovascular diseases (CVDs), hepatitis, and multiple sclerosis, which are untreatable and directly affect the county's economy and the development (Wieland et al. 2005; Ahmed et al. 2017; Kocher et al. 2018). Although the current population of the world uses modern therapeutic approach to treat these diseases, still many traditional practitioners use plant-derived products to treat, prevent, and cure these ailments. These are called herbal medicines (HMs). HMs have long history as most of the cultures throughout the world use HMs for the treatment of diseases from time immemorial (Sahoo et al. 2010). It is estimated around 25% of the drugs launched worldwide and more than 70% population of the developing countries basically rely on plant products for their preliminary health care or as a supplement for health (WHO 2002; Sahoo et al. 2010). According to WHO, it has been estimated that 250,000–500,000 species of plants exist on the earth, up to now, only around 10% or 21,000 plants have been used as medicines by humans to treat these complications. Among them, more than 200 species are found only in India; however, only 150 species are being used commercially as medicinal plants (Seth and Sharma 2004). In 2005, the global market of herbal drugs was worth an estimate of $18 billion, which was extended to nearly $19 billion in 2006 and more than

$26 billion by 2011 and subsequently increases according to demands (McWilliams 2006; Saklani and Kutty 2008). Nowadays, HMs have been trending as alternative or complementary medicines in view of their safety profile, cost effectiveness, strength, effectiveness, and ecofriendly therapeutic potential. Many plant-derived bioactive compounds, such as paclitaxel and camptothecin from *Taxus brevifolia* and *Camptotheca acuminata* having anticancerous, artemisinin from *Artemisia annua* bearing antimalarial, forskolin from *Coleus forskohlii* against obesity and arthrosclerosis, antidiabetic compound steviol from *Stevia rebaudiana*, galantamine from *Galanthus nivalis* against Alzheimer's, and apomorphine, a semisynthetic analogue of morphine derived from *Papaver somniferum* with Parkinson's treating properties, have been well explored and reported since last few decades (Veeresham 2012; Boyle and Ondo 2015; Jain and Jain 2018; Zaidan et al. 2019). In spite of their appreciated potential against different human diseases, their exploration as medicine directly to human has faced several challenges due to lack of scientific and clinical evidence regarding their biochemical mode of action on particular cells, tissues, or organs as well as standardization issues. Based the aforementioned background, the present chapter deals with exploration of some important medicinal plants for the development of drugs, which are useful for treatment of severe human's ailments. Further, the chapter provides an emphasis on therapeutic properties of these HMs with possible mechanism of action against important diseases, and at the end, the safety profile of HMs has been incorporated so as to exploit them as an alternative medicine in the era of modern therapeutic approach.

2.2 Traditional Knowledge of Herbal Medicines (HMs)

The humans have used plant products since antiquity to relieve and treat the diseases. Some fossil records reveal that humans were using plants to cure diseases back at least 60,000 years (Fabricant and Farnsworth 2001; Shi et al. 2010). The knowledge of thousands of years of traditionally used herbal medicines can be used to overcome several medical problems of present generations. The development of medicine for the early humans was not an easy task; several of them have sacrificed their lives during the course of testing of plants with some beneficial medicinal importance. Some plants might be poisonous, harming their lives. HMs are still the centerpiece as about 80% population of developing countries requires them for the primary health care due to lesser side effects, cultural acceptability, higher efficacy, and availability (Gupta and Raina 1998; Kamboj 2000; Ekor 2014). Medicinal plants are the major source of traditional medicines as well as some modern medicines. The earlier records of HMs suggest their use for 5000 years in Greek, Chinese, Indian, Egyptian, Roman, and Syrian literature (Pal and Shukla 2003). The old texts of India such as Atharvaveda, Rigveda, Sushruta Samhita, and Charaka Samhita deal with HMs, and all these were derived from very rich scientific devise and early civilization (Kamboj 2000). Many forms of traditional HMs exist in the world; some of which are listed as follows.

2.2.1 Ayurveda

Ayurveda is one of the ancient medicinal systems of Indian civilization since prehistoric time. Etymologically, Ayurveda is the combination of two Sanskrit words "Ayur" meaning life and "Veda" dealing with science or knowledge, which means "the science of life." The philosophy behind Ayurveda is living a long life without unnecessary suffering and bringing balance as well as consonance between three paradigms of life, that is, spirit, mind, and body. Ayurveda is considered as holistic in sense that it balances and integrates the spirit, body, and mind to cope with illness and some diseases. On the basis of origin of medicines, Ayurvedic medicines are divided into three categories which are herbal, mineral, and animals. Among all, HMs gained a great deal of attention due to their safety profile (Parasuraman et al. 2014). The Indian subcontinent is one of the mega biodiversity centers with about 45,000 plant species, which contribute to be a reservoir of herbals (Hasan et al. 2009). From India, about 15,000 medicinal plants have been documented, out of which 7000 are being used by several communities for curing different kinds of diseases, and there are almost 700 types of plants listed in the Ayurvedic system of medicine (Meena et al. 2009).

2.2.2 Traditional Chinese Medicines (TCMs)

This originated thousands of years ago in China. It comprises of four elements: monarch, minister, assistant, and servant according to their roles in the formula. TCMs are based on the concept of Yinyang and Wuxing, and formula includes a group of several kinds of drugs which function together to show a synergistic action. TCMs are a part of people medicine system in China. In recent years, TCMs have gained an approval to be used as alternative and complementary medicine in Western countries also. It is estimated that about 1.5 billion people are being cured by TCMs throughout the world (Dobos et al. 2005; Qi et al. 2013). TCMs are being used in the treatment of allergic responses along with some other diseases which put burden on the economic trade due to poor health condition of the country (Lin et al. 2019). The pharmacology of TCMs has evolved with time, and several scientific communities are trying to make an effort to understand the molecular mechanism of action of TCMs so as to incorporate these formulation into modern medicines.

2.2.3 Kampo

Kampo evolved around fifth and sixth century in Japan, and it came into existence from China via the Korean peninsula. It focuses on patient as a whole in place of the disease only. TCMs were altered and some new modifications were done accordingly and adapted by the Japanese medical practitioners which evolved as Kampo (Yakubo et al. 2014). The herbal formulations of Kampo medicine system are being governed in the same way as that of the other conventional medicines of the world,

and it is considered to be safe. Currently, about 90% of the medical professionals in Japan prescribe Kampo medicine in spite of Western medicines. Physicians in Japan use Kampo medicine with chemotherapy or radiation therapy for the treatment of patients suffering from cancer (Okamoto et al. 2014; Sahashi 2005). Kampo medicine system does not discriminate the symptoms as physical and psychiatric; the reason behind such concept is the thought of the Kampo system which considers human beings a complete, self-controlled unit. Both body and mind control each other and get affected by each other.

2.2.4 Unani Medicines

This is an important traditional HM system, popular in India and originated from Greek- Arabic medicine system around 2000 years back in Arabian civilization. In this system of treatment, whole body is treated as a single unit and its mind, soul, and body as a whole (Lone et al. 2012). Unani medicine is also recognized by WHO as alternative medicine system for curing the sufferers. The body temperature of a human being shows its well-being and mental and physical status. Alteration in the body temperature makes the human body susceptible to many kinds of diseases. Many of the bioactive components of mangrove forests have been isolated and being used in Unani medicine system since long time (Govindasamy and Kannan 2012; Jabin 2011).

2.2.5 Russian Herbal Medicines

This originated in Russia in the tenth century and was also introduced in Europe and Asia. Russia has large size of land and variety of soil composition which favors the growth of large numbers of medicinally important plants. So, herbal medicine is quite popular out there. A recent survey done by an authority found that about 44% people of Russia use HMs occasionally and about 12% use it frequently (Shikov et al. 2014). There is a separate branch of phytotherapy in Russia for the treatment of patients.

2.2.6 Africa Traditional Herbal Medicines

It originated in Africa and was based on holistic view of HMs which inherited from rich cultural heritage. About 80% people of Africa use herbal medicines to get rid of the disease (WHO 2002). The herbal medicines are easily accessible by the people of Africa, so this remedy is the most popular one in that area. The traditional medicine system is well integrated in the scheme of national healthcare system of the country and well organized (Boakye et al. 2015).

2.2.7 Traditional Medicines of Korea: Sasang Constitutional Medicines (SCM)

It was first introduced in nineteenth century in Korea, and SCM is also a part of Korean traditional medicine. A Korean medical doctor named Lee proposed the concept of SCM about 100 years ago. SCM is very holistic and patient specific, and every patient may be categorized into one, on the basis of inherited characters out of four Sasang Constitution (SC). The four types of SC are TaeEum (TE), So-Eum (SE), So-Yang (SY), and Tae-Yang (TY). The TE (TY) type is called liver (lung) type. The other two, SE and SY are called kidney and pancreas types, respectively (Kim et al. 2013). It is applicable in private and public hospitals in Korea. In 2006, the scientific proof of SCM was provided by Lee Jama project and also taken cared by the government of Korea.

2.3 Past, Present, and Future Scenario of Human Disease Prevention by Plant Products

Plant products are the natural source of several biologically active substances, which encompasses different properties that play major role in disease prevention caused either by biological or by non-biological agents. It has been proven that allopathic medicines are more toxic to the nontarget tissues and alter some other related biological activities and are more expensive. On the other hand, HMs show lesser or no side effects and are available in affordable price too (Alzohairy 2016). Plants have several secondary metabolites in the form of phytochemicals which protects plants from invasion of pests and infection from microorganisms. These phytochemicals have some active ingredients which can be used in the form of drug for the treatment and prevention of disease (Shakya 2016). Phenolic compounds of plants are most valuable among the secondary metabolites because of their active role in morphological development, reproductive process, and physiological responses. There are about 8000 structures of different plant phenolic compounds known to us. The central skeleton of phenolic compounds is formed by one phenolic ring, and hydrogen is replaced by more active residues like hydroxyl, acetyl, and methyl groups. This is the reason behind wide spectrum of biological properties of phenolic compounds. In plants, these phenolic compounds are assembled in phenolic rings and are called polyphenols (Del Rio et al. 2013; Laura et al. 2019). Phenolic compounds containing plants have high antioxidant properties. Plants absorb the radiation of sun and produce oxygen as a by-product. Oxygen gets activated by UV light and heat generated by sunlight and produces reactive oxygen species (ROS), which interfere with cellular entities and alter them leading to cellular damage (Singh et al. 2019). Many studies show that high amount of consumption of fruits and vegetable containing phenolic compounds reduces the risk of diabetes and risk of cardiovascular diseases (Nöthlings et al. 2008).

2.4 Prevention of Important Diseases Using Herbal Medicines (HMs)

Prevention of infectious as well as noninfectious diseases in healthcare setting is the primary goal of the medical authority throughout the world. There are several diseases caused by microbial (bacterial, fungal, and viral) infection while others are caused due to disregulation of primary metabolic and body defense systems, which are evolved to protect body from suffering. There are many examples, where plant products have made their irony contribution toward disease management (Mitchell et al. 2016). Some of the important untreatable diseases and their possible preventive measures reported using plant products are discussed below in the following sections.

2.4.1 HMs Against Malaria

Malaria is considered as the disease of global importance with more than 3 billion people in tropical and subtropical countries are at risk with the estimated death of 6 lac as recorded by World Health Organization in 2015 (Cowman et al. 2016). The infection initiated when sporozoites produced by *Plasmodium* spp. enter the host body through female anopheles mosquito vector feeding human blood. The accompanying chronic symptoms appear in the form of rigors, nausea, headache, body pain, etc. The first affordable and safe plant-derived compound discovered in 1820 against malaria was quinine, which was obtained from the bark of *Cinchona* tree found abundantly in high altitudes of the South Africa (Achan et al. 2011). In 1940, another antimalarial drug called chloroquine was synthesized and used for the treatment of malaria; however, due to their synthetic origin, the pathogen develops resistance, which was more problematic (Mukherjee 1991). At the same time, a group of Chinese chemists extracted the drug artemisinin from the warm wood plant *Artemisia annua*, which has proved to be very effective against both the chloroquine-resistant and chloroquine-sensitive *Plasmodium falciparum* pathogen (Spooner and Harvey 1976; Meshnick and Dobson 2001). Krettli et al. (2001) reported the antimalarial property of freshly prepared extract of *Bidens pilosa* and *Ampelozizyphus amazonicus* against erythrocyte stage sporozoites of *Plasmodium*. In addition, the essential oil obtained from the leaves and stems of some plants like *Myrtus communis* and *Rosmarinus officinalis* was reported to inhibit the active growth of *Plasmodium falciparum* under in vitro condition (Milhan et al. 1997; Hennia et al. 2019). Later on many other plants such as *Azadirachta indica*, *Asparagus africanus*, *Bixa orellana*, and *Clerodendrum viscosum* as a whole or some plant parts such as leaf of *Jasminum syringifolium*, root of *Plumbago zeylanica*, flower of *Corymbia watsoniana*, seed of *Cuminum cyminum*, and the fruit of *Citrus limetta* have been well explored and reviewed for their potential antimalarial properties (Kaur and Kaur 2017). In addition, some plant-specific compounds like vasacine from *Adhatoda vasica*, barberine from *Berberis aristata*, calusamine from *Clausena anisata*, caesalpin from *Caesalpinia sappan*, piperine

from *Piper nigrum*, and tinosporine or withanine from *Tinospora cordifolia* and *Withania somnifera*, respectively, showed antimalarial properties (Sankhala et al. 2012; Uddin et al. 2012; Damanhouri and Ahmad 2014; Kaur and Kaur 2017).

2.4.2 HMs Against Diabetes

Diabetes is a class of metabolic syndrome rather than disease characterized by low glucose level in blood due to alteration in insulin secretion, insulin action, or both from the β-cells of pancreas affecting large number of people throughout the world (Patel et al. 2012). Generally, it is evident that the diabetic people have more chances of cardiovascular attacks than the nondiabetic ones (Kannel and McGee 1979). Up to now only plasma-mediated transfusion of drugs are available to treat diabetes due to their sensitivity toward digestive enzymes, which inactivates them upon consumption when taken through oral routes; therefore, it is desirable to think toward some oral form of alternatives. In this context, plants can be the best alternatives, and more than 800 plants are available and reported to show antidiabetic properties without causing any complication (Trojan-Rodrigues et al. 2011). *Eugenia jambola*, a plant from family Myrtaceae was reported to contain many phytochemicals such as ellagic acid, isoquercetin, kaempferol, myricetin, and alkaloid jambosine, which all exhibited antidiabetic action upon consumption (Ayyanar and Subash-Babu 2012). Whole plant part of holy basil (*Ocimum sanctum*) was reported to show antihyperglycemic effect, and after their chemical standardization, it was found that the antidiabetic action of this plant was due to eugenol (Pattanayak et al. 2010). *Stevia rebaudiana*, which was reported to be more than hundred times sweeter than the sugar, possesses hypoglycemic action in diabetic patients (Shivanna et al. 2013). Likewise, many more plants such as *Aegle marmelos*, *Acacia arabica*, *Andrographis paniculata*, *Aloe barbadensis*, *Juglans regia*, *Momordica charantia*, *Terminalia chebula*, *Tinospora cordifolia*, and *Withania somnifera* were reported to show antidiabetic action either due to dowregulation of the blood glucose level by improving the action of insulin or by some other metabolic functioning (Stanely et al. 2000;, Kumar et al. 2006; Udayakumar et al. 2009; Tripathi and Chandra 2010; Naveen and Baskaran 2018).

2.4.3 HMs Against Cancer

According to an estimate of WHO, more than 200 different types of cancer have been identified, and cancer is considered as one of the second leading causes of death throughout the world (Bray et al. 2018). Several chemopreventive measures have been undertaken to treat cancers; however, their cost effectiveness and adverse effects on healthy cells or tissue restrict their successful utilization. To combat these effects, many plant-derived compounds like vincristine from *Catharanthus roseus*, taxol from *Taxus brevifolia*, camptothecin from *Camptotheca acuminata* have been well documented in literature to show their broad term action against

cancer or cancer cell lines under in vitro condition. The possible mechanism of action of taxol was believed to occur due to arrest of cells in G2/M phase of the cell cycle, while camptothecin exhibits their action by inhibiting the activity of topoisomerase I enzymes involved in DNA replication (Yeung et al. 1999; Liu et al. 2000). Several other compounds like topotecan, irinotecan, docetaxel, podophyllotoxin, teniposide, and elliptinum have been documented to showed anticancerous properties (Cragg and Newman 2005). Although they possess novel mechanism of action against different cancer cell lines, in order to recommend or commercialize them as possible alternative to the harmful and costly anticancerous drugs, it is desirable that the scientific community should work more on their action.

2.4.4 HMs Against Alzheimer's and Parkinson's

Alzheimer's and Parkinson's have been considered as the most prevalent form of late life mental complications in humans due to irreversible loss of neurons. The clinical symptoms of Alzheimer's appear in the form of impairment in memory, judgment, decision making, orientation to physical surroundings, and language, while Parkinson's showed symptoms in the form of Parkinsonism, that is, resting tremor, bradykinesia, rigidity, and postural instability (Hoehn and Yahr 1967; Nussbaum and Ellis 2003). One of the most promising approaches used to treat the Alzheimer's and Parkinson's is to increase the level of acetylcholine by acetyl cholinesterase inhibitors. Several plant-derived bioactive compounds like galanthamine, donezepil, rivastigmine, physostigmine, and morphine have been reported to act as potential inhibitor of acetylcholine and therefore help in the treatment of Alzheimer's complications (Barbosa Filho et al. 2006; Saklani and Kutty 2008). Some other approaches have also been hypothesized; however, due to lack of authentic evidences, the complete cure of these neurodegenerative disorders remains unresolved.

2.4.5 HMs Against HIV

AIDS is a well-known sexual disorder causing mortality and morbidity throughout the world. Since its discovery, there are no effective vaccines developed to cure HIV infection. The antiretroviral therapy is the most significant approach used for their treatment, and it is recommended that all patients with detectable HIV infection should be treated with antiretroviral therapy to prevent their subsequent progression as well as to reduce transmission (Günthard et al. 2016; Salehi et al. 2018). Several plants such as *Artemisia annua*, *Astragalus membranaceus*, *Calendula officinalis*, *Chelidonium majus*, *Galanthus nivalis*, *Helichrysum populifolium*, and *Hypericum perforatum* have been tested and reported for their antiretroviral properties against HIV infection. *Galanthus nivalis* performed its action by preventing the binding of viral envelop protein to the host cell's receptor, therefore inhibiting host-specific recognition (Magadula 2010). Some others like *Chelidonium majus* and *Calendula*

officinalis showed their action by preventing infection of CD^{4+}-T cells and inactivating the action of viral-specific reverse transcriptase (Asres and Bucar 2005; Salehi et al. 2018).

2.4.6 HMs Against Bacterial Food Poisoning and Fungal Mycotoxicosis

Several species of bacteria like *Staphylococcus*, *Clostridium*, *Campylobacter*, *Shigella*, and *Bacillus* as well as fungi such as *Aspergillus*, *Fusarium*, and *Penicillium* have been reported to produce most frequent group of bacterial and mycotoxins in food items, which upon consumption can cause severe case and food-borne poisoning and mycotoxicosis. The important disease caused by bacteria include diarrhea, tuberculosis, typhoid, and many more, while fungi caused mycotoxicosis, which is characterized by immune suppression, liver cirrhosis, abnormal fetus development, stunted growth, and sometimes cancers (Newell et al. 2010; Dwivedy et al. 2017; Chaudhari et al. 2019; Hashempour-Baltork et al. 2019). Different chemical preservatives and shelf life enhancers have been used since long time to eradicate these contaminants and their toxins; however, their indiscriminate use may lead to the development of resistance stain of these contaminants and residual toxicity to the nontarget organisms and to the environments (Linke et al. 2018; Chaudhari et al. 2019). In this context, many authors have claimed the importance of plant-derived essential oils (EOs) and their bioactive compounds as safer candidate for the preservation of these food items. Some of the important essential oils showing broad term toxicity against food-borne bacterial and fungal pathogens are allspice EO isolated from *Pimenta dioica*, lemon balm EO from *Cistus ladanifer*, basil EO from *Ocimum sanctum*, rosemary EO from *Rosmarinus officinalis*, citrus EO from *Citrus citrata*, mint EO from *Mentha spicata*, and *Cymbopogon citratus* (Chao et al. 2000; Burt 2004; Prakash et al. 2012; Kedia et al. 2016; Chaudhari et al. 2018; Upadhyay et al. 2018). These EOs contain different bioactive components, and each of them has different mode of action; therefore, the development of resistant strain among pest's population is hindered, and hence it is recommended as the safer alternative to the chemical preservatives for the preservation of food items from bacterial and fungal contamination as well as against their toxic metabolites.

2.4.7 HMs Against Tuberculosis

It is estimated that throughout the world, around 8 million people are suffering with the death of around 2–3 million due to tuberculosis. Although few slow working drugs are available against tuberculosis causing bacteria, development of resistance due to their multiple uses may further increase the risk (Keshavjee and Becerra 2000). To combat this issue, finding new drugs which have desirable capacity to fight with multiple sites of action is required; therefore, several tremendous researches throughout the world by different groups of scientists have been carried

out in the search of novel anti-tuberculosis agents of plant origins. Several reports are available regarding the anti-tuberculosis activity of plants such as extracts of *Curcuma longa*, *Allium cepa*, *Terminalia glaucescens*, *Leucophyllum frutescens*, *Chrysanctinia mexicana*, and *Schinus molle* (Newton et al. 2002; Molina-Salinas et al. 2007; Ibekwe and Ameh 2014); however, despite of their novel activity against tuberculosis and their causing agent *Mycobacterium tuberculosis*, none of the drugs are currently being used due to lack of scientific evidence and standardization of their exact mode of action. Hence, it is suggested that the scientists should work more on their mechanism of action, so as to utilize them as possible candidate for the prevention of tuberculosis.

2.4.8 HMs Against Epilepsy

After Alzheimer's and Parkinson's, epilepsy is the third important class of serious brain disorder occurring in people of all age groups from childhood to old. Currently, many of the used drugs suppress epileptic seizures without influencing the underlying tendency to generate seizures and are effective in more than 70% of individuals tested (Duncan et al. 2006). A lot of plants, namely, *Hypericum perforatum*, *Ginkgo biloba*, *Allium sativum*, *Piper methysticum*, *Illicium anisatum*, *Ephedra sinica*, and *Bacopa monnieri*, have been used by patients without consultation of physician to treat epilepsy (Samuels et al., 2008; Schachter 2009). Although these plants and their bioactive principles possess therapeutic properties against epilepsy, however, they also have some adverse effects as many of them induce seizure due to the neurotoxic action of their active principles; hence, it is recommended to utilize these plants or their derived products only after complete profiling and pharmacological action recognition by the experts.

2.4.9 HMs Against Hepatitis

Hepatitis is a serious complication of liver caused mainly by hepatitis virus or toxic substances (alcohol, drugs, or aflatoxin) or due to immune suppression. It is also believed that aflatoxin along with hepatitis virus is the serious cause of liver cancer (Henry et al. 2002). Several antiviral proteins (interferons) are developed, and currently two important proteins that is, pegylated interferon-α (PEG IFN- α) and ribavirin (RBV) have been in use to treat this hepatitis; however, they have certain limitations based on genotype, which could force the scientist to develop antiviral proteins without adverse effects. In the last two decades, herbal formulations have been proven to act as effective strategies, and many plant bioactive compounds, namely, epigallocatechin gallate from tea, quercetin from onion and apple, acacetin from black locust, and genistein from bean plants have been proved to have antiviral and hepatoprotective properties (Loa et al. 2009; Stagos et al. 2012; Rojas Rojas et al. 2018). These substances can inhibit the proliferation of virus either by altering their genetic machinery or inhibiting them to bind with the receptor proteins present

on the host surface. Due to their activity relationship with aflatoxins, it is also possible to reduce the chances of hepatitis infection by inhibiting the level of aflatoxins. In this respect, many plant products, especially EOs, have been reported to show anti-aflatoxigenic properties, and thus foods preserved with EOs are free from aflatoxins. The consumption of these foods may passively reduce the chances of hepatitis.

2.4.10 HMs Against Multiple Sclerosis

Multiple sclerosis is a common non-injurious T-cell-mediated disability arising due to inflammation, demyelination, and axonal injury or due to childhood obesity, low level of vitamin D, smoking, or infection by Epstein–Barr virus (Dobson and Giovannoni 2019). Current marketed drugs for multiple sclerosis therapies include different injectable compounds such as interferon beta, glatiramer, and natalizumab as well as oral drug formulations like fingolimod, dimethyl fumarate, and teriflunomide (Brandstadter and Sand 2017; Guarnera et al. 2017; Yu et al. 2019). None of the medicines discovered till date have been reported to completely reverse multiple sclerosis; however, sometimes it is believed that the utilization of plant-derived compounds can be the effective strategies, and this may restore the functioning of neurons inflammation. In this regard, some important plants and their derivatives have been used and reported by many workers against multiple sclerosis. For example, cannabinoides from *Cannabis sativa*, icariin from *Herba epimedii*, plumbagin from *Plumbago zeylanica*, salvianolic acid from *Salvia miltiorrhiza*, eriocalyxin from *Isodon eriocalyx* (Ingram and Pearson 2019; Yu et al. 2019).

2.5 Complementary and Alternative Medicine (CAM): Modern Technological Platform for Reverse Pharmacology

Traditional medicines based on the herbal materials have now been clustered into "complementary and alternative medicines" with integrative health benefits and significant pharmacological properties, especially, the drugs derived from botanical formulations made of plant extract, aromatic essential oil profile, powders, and whole parts with different health benefits such as anticarcinogenic, anticonvulsant, antipyretic, and vasodilatory actions (Patwardhan et al. 2008). Recent report suggested that approximately 75% of the world population relies on the application of medicinal plant-based formulation in different health and healing effects. Newman and Cragg (2007) focused on the utilization of 47% of natural medicinal plant products in the major areas of cancer research. Different national and internationally recognized pharmacopoeia's have focused on the safety evaluation of these natural drugs with their potential therapeutic effects. Now, in the era of current generation, different accidental serendipity of excessive dose of plant drugs was also reported from different regions of the world, which ultimately led to a common

decision on their dosage identification and advanced combinatorial medicinal chemistry and system biology (Takenaka 2001).

Recently, the trends on medicinal plants research have a specific paradigm shifting with major biotechnological approaches and post marketing innovations on multiple modes of action. Pharmacological industries have faced critical challenges for practical application of medicinal drugs in terms of their safety issues and expenses (Surh 2011). Modern scientific communities and medicinal boards have decided a fast track platform with trans-disciplinary innovations on "Reverse Pharmacology" to improve the cost, toxicity exposure, and time management. Patwardhan and Mashelkar (2009) reported the documentation of medicinal formulations and group lineage through modern "Omic" technologies facilitating the transcriptomics, metabolomics, and operon dynamics. The modern dynamic technologies have moved on opposite directions of the traditional herbal cure methodologies with much faster reverse pharmacological approaches (Takenaka 2001). Screening, standardization, and modified clinical observation have biodynamic and exploratory potentiality for optimizing the level of acceptability and bio-accessibility. Moreover, the reverse pharmacology also signified the selective bioprospection of active constituents of plant parts and exclusion of poisonous ingredients with safety issues (Singh et al. 2018). Potential interest on active components of medicinal plants and their targeted mode of action having technological advances were first reported by Sir Ram Nath Chopra and Gananath Sen with documented discovery of tranquilizing and antihypersensitive agents from *Rauvolfia serpentina* (Patwardhan et al. 2008). Recently, the developing countries have developed "drug act" for the inclusion of active phyto-ingredients of different medicinal plants with pluralistic and opportunistic healthcare complexes (Rajapakse and Davenport 2019).

The process of reverse pharmacology follows targeted proteinaceous action and emerging dimension in sequence technology with target mining actions. Distant homologies and ligand fishing can be identified during drug moderation, and mechanistic basis of indexed biological processes is involved (Cavalli et al. 2008). It is an inter-bridging community between the molecular genomics and pathophysiology for the development of superior drug candidate. Today, there is actual need of linkage between Ayurvedic pharmacokinetics and modern systemic therapeutic approach which endeavors the direction for development of novel drugs. In India, Research and Development (R&D) authorities, Council of Scientific and Industrial research (CSIR), and Ministry of AYUSH actively participate in this direction and standardize several protocols for successive identification of plant parts and their rational drug development.

Case studies on *Withania somnifera* have suggested the significant modulation on the toxicity of cyclophosphamide and lipid peroxidation of stressed animals as well as chemo-protectant activity of the compound methylguanine DNA methyltransferase (MGMT) (Niture et al. 2006). Root extract of *W. somnifera* contains glycowithanolides as a protective measure against iron toxicity. Mechanistic details of *W. somnifera* fruits on interferon, interleukin, and macrophage-modulating factors have also been studied (Davis and Kuttan 1998). Flavones,

isoflavones, and saponins of *Asparagus racemosus* exhibited active inhibition of neuromuscular disorders, macrophage modulatory activities, and myelo-suppressive effects. Extracts of the dried roots caused targeted inhibition of neuroendocrinal effects (Dahanukar and Thatte 1988). Tumor necrosis factor-α and interleukin-1 stimulation by ochratoxin have been actively modulated by bio-components of *A. racemosus*. Different antioxidative compounds such as plumbagin, silymarin, and glycyrrhizic acid have been isolated from roots of *A. racemosus* with significant antitumor and cytotoxic activities (Patwardhan et al. 2008). Different active ingredients, namely, cordifoliside, columbin, berberine, and cordioside isolated from *Tinospora cordifolia* exhibited potent free radical scavenging, antipyretic properties, and modulate metabolic enzymes of liver. Bio-ingredients of *T. cordifolia* actively inhibited chloroquine-induced splenomegaly in mice (Singh 2005). Alkaloids, namely ajmaline and reserpine, and several active biocomponents such as bromoergocryptine and L-Dopa extracted from *Rauvolfia serpentina* inhibited depression and toxicity in human and modulated ATP-dependent cellular metabolism at the transcription level (Patwardhan et al. 2008; Singh 2017). Currently, the effect of alkaloids on H-2 receptor, inflammation inhibitory, and pharmaco-vigilance activity has been the focus of different researchers throughout the world. The *Argemone mexicana* decoction, which is in progress of being approved for the preparation and utilization as an antimalarial drug in Mali (Willcox et al. 2011). Different phytomedicines (P-glycoproteins, allocryptopines, and berberine) prepared through synergistic and additive activities of extracts of *Artemisia annua*, *Argemone mexicana*, *Withania somnifera*, and *Cassia auriculata* with effective drug phramacokinetics have been utilized as traditional remedial measures (Willcox et al. 2011; Visavadiya and Narasimhacharya 2007; Annie et al. 2005). Bioactive pharmacological ingredients extracted from *Commiphora wightii* (guggul) exhibited different cellular and molecular level pharmacodynamic and pharmacokinetic properties in human (Vaidya 2006; Shishodia et al. 2008). Technological advancement through proteinaceous metabolites of *Commiphora* extract modulates the hypolipidemic profile in animals and human being. Recent study of Upadhyay et al. (2013) suggested active participation of Picrosides I and II isolated from dried rhizome and roots of *Picrorrhiza kurroa* for inhibition of respiratory tract infection, renal disorders, and dyspepsia in different animal models. Steps involved in reverse pharmacology with the active participation of different bioactive components and biotechnological approaches are presented in a flow diagram in Fig. 2.1.

Moreover, in addition to different healthy aspects of reverse pharmacology, each and every country has now secured its traditional herbal knowledge through the guidelines of Intellectual Property Right (IPR) and developed a digital library and patent consistency. The traditional knowledge along with modern pharmacodynamics could integrate the knowledge of ambitious scientific innovation and novel clinical approaches.

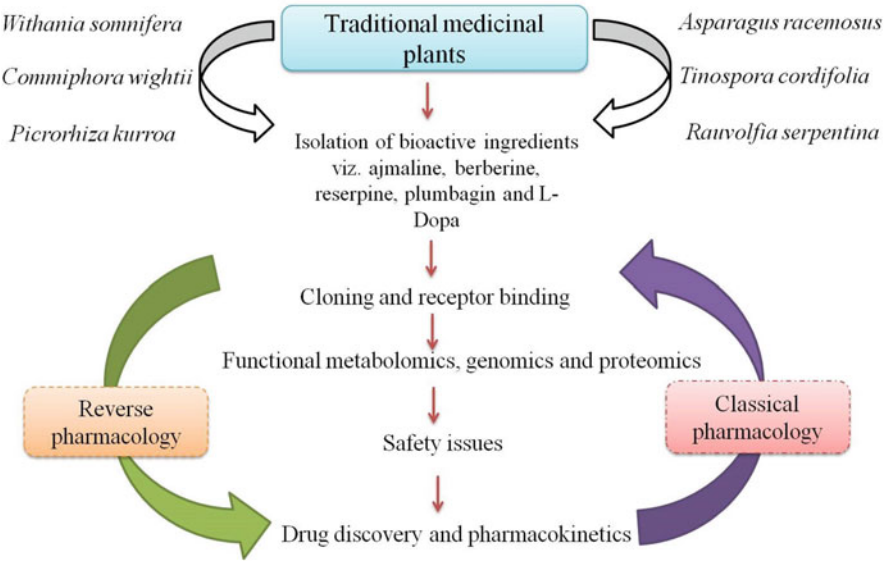

Fig. 2.1 Successive stages of reverse pharmacology involving the bioactive ingredients of medicinal plants and modern technologies

2.6 Safety Paradigm of Traditional Herbal Medicine

Herbal medicines are being used since very long time, and selection and cultivation of herbal medicines totally depend on the selection of right specimens. There are chances of alterations in the samples which could lead to a threat to consumer's health. In recent years, there is increase in the consumption of the herbal medicines due to its more safety values than that of allopathic medicines. So, it leads to greater chances of adulteration of herbal medicines (Zhang et al. 2015). Very less research has been done in case of safety of herbal medicines. Processing stage is the step where the herbal medicines can get contaminated even by slightly miss caring. Moreover, most of the natural products do not get proper evaluation at the laboratory level by the regulatory authorities, as result of which these products fail to prove their efficacy at the molecular level (Booker and Heinrich 2016). There are variabilities that are found in the herbal medicinal products at the inherited level. Also, variability is found at the batch-to-batch level, and absence of proper standard reference material also adds some more difficulties in the quality control assessment of herbal products (Ghosh 2018). It is believed that risks associated with herbal medicines are very low, but this is not the case, there are risks associated with the contamination in herbal products.

2.7 Conclusion and Future Prospective

From time immemorial, man has sought to prevent disease caused by different biological and nonbiological agents using various means among which the use of HMs containing different forms of plant secondary metabolites is very common. These HMs possess pharmacological activities against malaria, diabetes, Alzheimer's, Parkinson's, HIV, tuberculosis, hepatitis, cancers, multiple sclerosis, and many more caused by bacterial and fungal toxins without posing any desirable impact on body due to safety profile as approved by international as well as national authorities. In spite of their proved therapeutic potential, global utilization remains limited due to the fact that their mode of action and standardization were not tested during application. Further, by using reverse pharmacological tools, the promotion of HMs may be approved. Therefore, based on overall reports, this chapter concludes that the herbal medicines can be utilized as an alternative medicine after complete profiling and testing the exact mode of action.

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