Biodiversity and Therapeutic Potential of Medicinal Plants

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Abstract

The nature is the best combinatorial chemistry and possibly possesses solutions to all ailments for mankind. A strong body of evidence suggests that two-thirds of the world's herbal species harbor therapeutic values, and these plants have been used in the traditional system of medicine since the advent of human civilization. Various plant species provide a rich source of bioactive molecules/compounds (although many whose functions have not been meticulously investigated as yet) that are used to treat and prevent several human disorders all over the world. According to the World Health Organization (WHO), a large population (~80%) of developing countries depend upon the herbal medicines for its survival. The development of purified medicinal products from natural sources is encouraged since it is estimated that among thousands of plant species that exist in the world, only 10% have been explored to determine their pharmacological potential. Studies demonstrating the usefulness of various medicinal plants are being accomplished worldwide. These studies have reported that the bioactive compounds extracted from plants are generally effective in nature and possess high-quality, safety, and cost-effective profiles as compared to synthetic chemical drugs. Moreover, these plant derivatives are usually accepted across different

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cultures and ethnic groups. The field of "herbomics" which is at the infant stage of its development may help us in formulating individually tailored herbal interventions in this era of precision and personalized medicine. The aim of this book chapter is to provide an overview on the therapeutic and curative importance of different medicinal plants for treating common human diseases that include cancer, neurodegenerative diseases, major depressive disorder, bacterial and viral infections, and periodontitis. We believe that the natural products may be used as potential alternatives to standard drugs.

Keywords
Medicinal plants · Therapeutic potential · Bioactive compounds · Human diseases · Angiogenesis · Cancer · Infections

2.1 Introduction

Biodiversity contributes considerably toward human livelihood and growth and thus plays a predominant role in the welfare of the global population. According to a recent World Health Organization (WHO) report, a significant part of human populace (~80%) still depends on medicinal plants for meeting their need for basic healthcare. Natural substances such as digitalis (from foxglove), ergotamine (from contaminated rye), quinine (from cinchona), and salicylates (willow bark) have long served as sources of therapeutic medicines. Drug discovery from natural sources involves an intricate methodology that comprises of botanical, phytochemical, biological, and molecular techniques. Recent development in the molecular modeling and combinatorial chemistry has further stimulated the advancement of using phytochemicals in cure, control, and management of physiological, deficiency, infectious, and hereditary diseases. The field of "herbomics" is an exciting and evolving area of genetic science that may have long-term implications for developing precision and personalized medicine. The "herbomics" may help in understanding pharmacodynamics, pharmacokinetics, safety/toxicity profile, synergistic effects, and clinical efficacy of medicinal plants by decoding which genetic processes and molecular pathways are activated in an individual. The likelihood of side effects or inadequate response to a herbal medicine may also be evaluated.

Paradoxically, the potential benefits of plant-based medicines have led to unscientific exploitation and misutilization of the natural resources. This decline in biodiversity is largely responsible for the rise of rapid industrialization, indiscriminate deforestation, pollution, and fast changes in global climate in the past few years. Therefore, it is of utmost importance that plant biodiversity be preserved, to provide future structural diversity and lead compounds for the sustainable development of human civilization at large. This becomes even more important for developing nations, where well-planned bioprospecting coupled with nondestructive commercialization could help in the conservation of biodiversity.

In this brief chapter, we will present biodiversity and therapeutic potentials of different plant products involved in combating angiogenesis (a normal physiological process) and against various human diseases that include cancer, neurodegenerative disorders, major depressive disorder, bacterial and viral infections, and periodontitis.

2.2 Angiogenesis

The formation of new blood vessels from existing vasculature is defined as angiogenesis (Risau 1997). Angiogenesis is a normal process that has a central role in various physiological processes within human body. Angiogenesis also plays a crucial part in the pathogenesis of several diseases, including various kinds of cancers. Therefore, natural or synthetic compounds that target angiogenetic processes may help in successfully treating these cancers (Folkman 1996). At present, most of the antiangiogenic agents comprises of mostly synthetic chemicals or humanized monoclonal antibodies that specifically target tight regulation of multiple signaling pathways (Kubota 2012). Despite promising findings and significant progress, the role of synthetic antiangiogenic drugs has been limited secondary to high cost, serious systemic toxicities, and development of resistance necessitate associated with these drugs. Therefore, efforts should be made at identifying other novel and effective anti-angiogenic molecules that are inexpensive and have minimal or no side effects (Samant and Shievde 2011). A high number of studies have indicated that natural plant products such as alkaloids, terpenoids, tannins, and polyphenols have angiogenesis-modulating properties. For instance, Castanospermine, an alkaloid, is present in *Castanospermum australe*, and the pods of *Alexa leiopetala* is a glucosidase inhibitor (Clark et al. 2001). A previous research report (Pili et al. 1995) suggested that castanospermine suppresses migration and invasion of endothelial cells through the basement membrane. In addition, it has also been reported that this molecule prevents the morphological differentiation of endothelial cells by altering the structural arrangement of oligosaccharides present on their cell surfaces (Pili et al. 1995). Another bioactive compound, sanguinarine (a benzophenanthridine alkaloid), that is derived from the roots of *Sanguinaria canadensis* has been described to markedly suppress vascular endothelial growth factor (VEGF)-induced migration of endothelial cells in a dose-dependent manner process. Similarly, brucine, an indole alkaloid derived from *Strychnos nux-vomica*, inhibits VEGF-mediated angiogenesis both in vitro and in vivo by suppressing downstream protein kinases. Colchicine and vinblastine are two other biologically important alkaloids that are derived from *Colchicum autumnale* and *Catharanthus roseus*, respectively (Stafford et al. 2005). Although colchicine is an excellent source of stabilizing vasculature in vitro at a moderate concentration of 10^{-6}~10^{-8}M, the effective anti-angiogenic dose is reported to be toxic to humans, putting a question mark in their clinical applications (Stafford et al. 2005). However, a high-quality study reported that a continuous administration of vinblastine at an approximate dose of 2.0 mg/kg/week produces inhibitory effects on VEGF-mediated angiogenesis in mammalian models; nevertheless, the precise mechanisms underlying the anti-

angiogenic actions of these compounds are still undefined (Albertsson et al. 2008). Ginsenosides (a terpenoid) including ginsenoside-Rg3 and ginsenoside-Rb2 are found in the roots of red ginseng (*Panax ginseng*). These natural agents significantly are known to decrease the number of newly formed blood vessels in murine B16 melanomas. Taxol is a complex polyoxygenated diterpene that is isolated from bark of the Pacific yew tree (*Taxus brevifolia*). Taxol is a well-known and natural cancer drug possessing cytotoxic activities especially at low concentrations that ranges between 25 and 100 nM. This natural therapeutic agent is used in the treatment of breast, lung, and ovarian cancers. The proposed mechanism involves downregulation of VEGF expression and the upregulation of hypoxic induced factor-1 proteins (Escuin et al. 2005).

Polyphenols are members of a large family of chemical compounds that are found in several plants and fruits, including the catechins found in tea, curcumin in *Curcuma longa*, and resveratrol in grapes and berries (Manach et al. 2004). These natural compounds have antiproliferative effects. Resveratrol, a polyphenol present in grapes, berries, and other plant sources, affects tumor angiogenesis via many mechanisms (Brakenhielm et al. 2001). Using murine models of fibrosarcoma, some studies have suggested that oral administration of resveratrol might inhibit tumor growth by severely restricting endothelial cell migration, proliferation, and formation of new blood vessels. The most likely primary action mechanism of resveratrol is through the inhibition of FGF2 and VEGF receptor-mediated activation of MAPK in endothelial cells (Brakenhielm et al. 2001). Catechin derivatives, such as epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epigallocatechin-3-gallate (EGCG), are present in green tea (Wang et al. 2015). Thearubigins and theaflavins are found in black tea (Wang et al. 2015). Together, these compounds are known to inhibit both VEGF upregulation and capillary endothelial cell proliferation. In another study, EGCG was shown to inhibit migration of neutrophils and thus polymorphonuclear neutrophil-induced angiogenesis in a dose-dependent manner (Donà et al. 2003). Flavonoids, including flavones, flavonols, flavanones, anthocyanins, and isoflavones, comprise another class of polyphenols that demonstrate anti-angiogenic properties (Fotsis et al. 1997). Genistein, an isoflavonoid derived from *Genista tinctoria*, may prevent bFGF-mediated endothelial cell tube development by downregulating the expression of plasminogen activator factors (Fotsis et al. 1993).

Another example of natural product that has potent anti-angiogenic property is Triphala churna (THL) which is an equimolar mixture of three myrobalan fruits that comprises of *Emblica officinalis* Gaertn (Amla), *Terminalia chebula* Retz (Haritaki), and *Terminalia belerica* Roxb (Bibhitaki). Interestingly, recent studies have demonstrated that THL and particularly its active tannin compounds chebulinic acid and chebulagic acid significantly inhibit VEGF-induced angiogenesis by blocking VEGFR-2 phosphorylation (Lu and Basu 2015).

In conclusion, compared with currently available anti-angiogenic synthetic drugs, plant products not only have comparable therapeutic potential but more importantly are less toxic in nature, inexpensive, and easy to administer. However, novel and effective strategies are necessary to improve the bioavailability and processing of natural products for their optimal clinical use.

2.3 Cancer

Cancer is one of the most lethal diseases worldwide, and the incidences of various cancers are continuously growing in both developing and developed countries over the past several decades. The current standard of care to treat various cancers includes surgery followed by concurrent chemoradiation therapy. Despite multimodality therapeutic interventions, prognosis of patients with cancer is generally dismal. Even advent of strategies such as tumor-treating fields and immunotherapy has not substantially improved the disease-free and overall survivals of cancer patients. Therefore, development of novel, cost-effective, and efficient treatment methods is required. The anticancer characteristics of a number of plants are still being actively explored, and some herbs have even shown encouraging results. Many of the bioactive compounds have demonstrated potential antioxidant, antiproliferative, anti-inflammatory, and anti-angiogenic effects in the fight against several cancers. Emerging studies have also shown that plant-derived molecules may be used in targeting different signaling pathways for cancer drug discovery. Taken together, these studies have reported that compounds that modulate these oncogenic processes may be potential candidates for cancer therapy and may eventually make it to clinical applications in the near future.

Some of the most common plants harboring anticancer properties are discussed below:

(a) *Tinospora cordifolia* efficiently destroys HeLa cells in vitro, signifying its potential as an anticancer agent. In a seminal study, a dose-dependent increase in cell death was observed in HeLa cells treated with *T. cordifolia* extract as compared to the controls (Jageti et al. 1998) providing the foundation for future research. Additionally, the anticancer action of dichloromethane extract of *T. cordifolia* in the mice transplanted with Ehrlich ascites carcinoma has been demonstrated. *T. cordifolia* extract showed a dose-dependent increase in tumor-free survival with highest number of survivors observed at 50 mg/kg dose (Jagetia and Rao 2006).

(b) Betulin and betulinic acid are potential anticancer phytochemicals that are widely distributed within the bark and stem of *Z. nummularia* and have been shown to have antitumor activity. In fact, betulinic acid glycosides produce differential cytotoxicity, such that cancer cell lines are more sensitive than normal cells (Gauthier et al. 2006). Similarly, betulinic acid, a naturally occurring pentacyclic triterpenoid, shows selective cytotoxicity against a variety of tumor cell lines (Eiznhamer and Xu 2004). Betulinic acid has been suggested to hold anticancer properties through a variety of mechanisms that include induction of apoptosis (program cell death) by generation of free radicals and reactive oxygen species, inhibition of topoisomerase I, activation of the mitogen-activated protein kinase cascade, inhibition of angiogenesis, and modulation of progrowth transcriptional activators and aminopeptidase-N activity. Furthermore, it was shown that betulinic acid induces apoptosis via a direct effect on mitochondria. These processes may be responsible for the ability of betulinic

acid to effectively destroy cancer cells that are resistant to other chemotherapeutic agents (Eiznhamer and Xu 2004).

(c) *Centella asiatica* is another plant that has demonstrated its potential utility as an anticancer agent. The whole plant or its leaves are regularly used for their remedial activities. Partially purified fractions of *C. asiatica* inhibit the proliferation of transformed cell lines, including Ehrlich ascites tumor cells and Dalton's lymphoma ascites tumor cells (Babu et al. 1995). Importantly, no toxic effects have been noticed in normal human lymphocytes. Additionally, partially purified fractions of *C. asiatica* significantly suppress the rapidly dividing of mouse lung fibroblast cells in culture. Moreover, oral administration of *C. asiatica* extracts has been shown to slow down the development of solid and ascites tumors and increase the overall survival time of tumor-bearing mice. The mechanism underlying the antitumor activity of *C. asiatica* seems to be the inhibition of DNA synthesis (Babu et al. 1995).

(d) The plant-derived curcumin exerts potent anticancer effects in vitro and in vivo with its ability to inhibit cell proliferation in a wide range of tumors (Shao et al. 2002). The anticancer properties of curcumin are generally related to its capability to downregulate the expression of a number of genes such as NF-kappa B, activator protein 1 (AP-1), epidermal growth receptor 1 (EGR-1), cyclooxygenase 2 (COX2), lysyl oxidase (LOX), nitric oxide synthase (NOS), matrix metallopeptidase 9 (MMP-9), and tumor necrosis factor (TNF). Moreover, turmeric that contains curcumin as an important component is known to reduce the expression of various chemokines, cell surface adhesion molecules, cyclins, and growth factor receptors, including epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) (Aggarwal et al. 2003). In addition to its effects on gene expression, turmeric inhibits the activity of c-Jun N-terminal kinase, protein tyrosine kinases, and protein serine/threonine kinases. The anticancer properties of turmeric also inhibit tumor cell invasion and metastasis to the remote areas from the areas of tumor origin by reducing MMP-2 activity and by inhibiting HEp2 (epidermoid carcinoma cell line) cell invasion (Mitra et al. 2006).

(e) A landmark study reported that active constituents extracted from *P. amarus* plant result in a significant decrease in n-nitrosodiethylamine-induced tumor incidence (Jeena and Kuttan 1999). Additionally, a decline in tumor marker enzymes and liver injury markers has been reported. *P. amarus* extract has been shown to inhibit DNA polymerase of hepatitis B virus and related hepatitis viruses and has been shown to downregulate hepatitis B virus mRNA transcription and translation (Lee et al. 1996). It is also reported that the extract of *P. amarus* inhibits aniline hydroxylase, a P450 enzyme that is responsible for the activation of some carcinogens. In a study, it was found that the extract of *P. amarus* inhibited the activity of tyrosine phosphatase, a key enzyme involved in the regulation of cell mitosis. It was also observed that the extract of *P. amarus* resulted in the inhibition of the activity of topoisomerase I and II in *Saccharomyces cerevisiae* mutant cell cultures. Additionally, *P. amarus* extract has been reported to have anti-angiogenic effects in mice harboring Lewis lung carcinoma (Huang et al. 2006).

The role of phytochemicals as cytotoxic agents against cancer cell lines has frequently been reported. Various plant molecules including nutraceuticals, such as allicin, apigenin, berberine, catechin gallate, celastrol, curcumin, epigallocatechin gallate, fisetin, flavopiridol, gambogicacid, genistein, plumbagin, quercetin, resveratrol, silibinin, taxol, derived from spices, legumes, fruits, nuts, and vegetables have been shown to modulate inhibitory effects against tumor cells (Chirumbolo 2012). Several other molecules from medicinal plants are already clinically established for cancer treatment. These include alkaloids such as vinblastine and vincristine isolated from *Catharanthus roseus* (Gullett et al. 2010), combretastatins isolated from *Combretum caffrum* (Cirla and Mann 2003), paclitaxel obtained from *Taxus brevifolia* (Luduena 1998), camptothecin isolated from *Camptotheca acuminata*, and homoharringtonine isolated from *Cephalotaxus harringtonia* (Aboul-Enein et al. 2014).

The isoquinoline alkaloid, isotetrandrine isolated from *Xylopia aethiopica*, is among the most active alkaloids described. This compound has been shown to display interesting cytotoxic effects against several cancer cell lines. In a previous study (Kuete et al. 2015), this compound was not shown to modify the integrity of the mitochondrial membrane in CCRF-CEM cells. However, its mode of induction of apoptosis was chiefly by increased production of reactive oxygen (ROS) species.

Phenolics have been the most studied group of secondary metabolites isolated from medicinal plants. Several compounds such as benzophenones, flavonoids and isoflavonoids, naphthyl butenone, quinones, and xanthones with fascinating cytotoxic activities have been identified.

It is also widely accepted that cancer inhibition by natural dietary agents is perhaps one of the best strategies in preventative medicine (Kuno et al. 2012). Specifically, tea polyphenols can potentially affect numerous molecular targets that are known to relate with cell proliferation, thus inhibiting tumor cell growth. Green tea polyphenols composed mainly of gallocatechin, epicatechin, epigallocatechin, epigallocatechin gallate, and caffeine inhibit the mitotic rate and hence decrease the growth and viability of human hepatocellular carcinoma cells probably by inducing apoptosis in these cells in a dose-dependent manner (Hessien et al. 2013). The same effect has also been observed in an important study in which green tea extracts were reported to induce apoptosis in the cell lines of gastric carcinomas (Gonzalez 2014). This could be attributed to the fact that green tea works synergistically with other proteasome inhibitors to retard the growth of neoplastic cells.

There are many reports on the antitumor and cancer prevention activity of black tea and green tea. However, a meta-analysis (Tang et al. 2009) indicated that an increase in green tea consumption may lead to reduced incidences of lung cancers, while the similar effect of black tea was not found to be true. Analogous results were reported (Goldbohm et al. 1996) in a prospective cohort study, which suggested that the consumption of black tea did not have any protective effect against colorectal, lung, and breast cancer. However, we believe that these results may not necessarily negate the effect of black tea in other types of cancer such as ovarian cancer and bladder cancer in females in which positive anticancer effects were observed

(Wu et al. 2013). Collectively, these studies indicate that the combination of green tea with black tea may have a positive effect against cancer.

Black tea polyphenol combination with resveratrol has been reported to synergistically inhibit established skin tumor growth compared to either of these agents alone, showing a decrease in tumor volume and number. The combination of curcumin, a major polyphenol in turmeric spice and green tea catechin, exhibited a synergistic colon cancer-preventative effect (Xu et al. 2010). There is an observed benefit in combining green tea with herbs or other nutrients that have greater combined benefits than that of green tea extract alone. Li et al. (2010) determined the synergistic effect of theaflavin-3,3-digallate (TF3) from black tea and ascorbic acids on cell viability and cell cycles of the human lung adenocarcinoma cell line SPC-A-1 and concluded that the synergistic effect enhances anticancer activity.

In summary, medicinal plants provide a broad spectrum of sources for developing novel and potent anticancer treatments. We strongly believe that some of the aforementioned natural products will end up being marketed as herbal medicines in treating various cancers in the near future. However, more work is required in order to isolate useful compounds that can be used as anticancer drugs. Likewise, it will be important for investigators to understand the different cancer-developing pathways in order to recognize what proteins and genes are required to be targeted.

2.4 Neurodegenerative Diseases

Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) are chronic disorders of central nervous system (CNS) that are characterized by neuronal loss, axonal degeneration, demyelination, and gliosis. Several studies have demonstrated that physicochemical properties of some proteins are altered causing deposition of these misfolded proteins in the human brain leading to neuronal degeneration. Well-established as well as novel therapeutic agents have been explored and tested to treat patients with neurodegenerative diseases; however, these drugs provide only short-term symptomatic benefits. Therefore, natural molecules from the plants and other sources are being discovered to substitute available synthetic medicines. Now, it is well documented that phytochemicals from medicinal plants can provide better and safer alternatives to synthetic molecules.

Berberine (BBR), a multicomponent herbal preparation, belongs to the isoquinoline class of alkaloids. It is generally isolated from several plants including *Hydrastis canadensis* (goldenseal), *Berberis vulgaris* (barberry), *Coptis chinensis* (copies or golden thread), and *Berberis aristata* (tree turmeric). It is recognized that BBR has several pharmacological effects like anti-inflammatory, antihypertensive, antioxidant, antidepressant, anticancer, antimicrobial, anti-diarrheal, cholesterol, and glucose-lowering properties. A few studies have reported that it is useful in a number of neurodegenerative disorders. BBR also possesses monoamine oxidase (MAO)-inhibiting property (Panahi et al. 2013) as well as AChE-inhibiting property as both are involved in the advancement of AD. In PD disease, BBR enhances the motor

stability and synchronization by inhibition of neuronal damage of dopaminergic neurons. It also improves short-term memory by inhibiting apoptosis and improving neurogenesis in dentate gyrus of hippocampal region (Huang et al. 2017). It was also observed that BBR significantly prohibited both balance and memory loss in PD patients and there was a constant decline in substantia nigra (SN) dopaminergic neuronal loss and rate of apoptosis processes in the hippocampus.

Morphine is an opiate alkaloid which exhibits widespread narcotic and analgesic effects and is used in the reduction of both acute and chronic pain. Morphine mediates its analgesic activity through the μ-opioid receptor (Kaur and Arora 2015). Various experimental models have revealed that morphine can exhibit beneficial role against CNS disorders (Ye et al. 2014). It is well documented that morphine plays a vitally important role in the treatment of AD through binding to MOR which increases the levels of gamma-aminobutyric acid (GABA, a neurotransmitter) in the synaptic clefts. This mechanism provides protection from oxidative stress mediated neurotoxicity (Cui et al. 2011).

Montanine is an isoquinoline alkaloid belonging to Amaryllidaceae family which is isolated from an ornamental plant named *Hippeastrum vittatum* (Moraga et al. 2016). It possesses anticonvulsant properties. Alongside, AChE-inhibiting activity of montanine has been reported. However, dose-response relationship is not fully known.

Salsoline is an isoquinoline alkaloid belonging to Chenopodiaceae family (Pagliosa et al. 2010). The genus *Salsola* (Chenopodiaceae) is known to include more than hundred species mainly found in moderate and subtropical areas of several countries. It is considered to possess neuroprotective potential through its cholinesterase inhibitory action and is frequently used to treat patients with AD.

Another natural product, piperine (PIP), is a chief alkaloid found in long pepper (*Piper longum*) and black pepper (*Piper nigrum*). It belongs to the Piperaceae family (Ghavami et al. 2014). It has been reported that piperine possesses a multiplicity of pharmacological effects which include anti-inflammatory, antifungal, insecticidal, antihypertensive, antipyretic, antitumor, and analgesic effects. Additionally, it possesses many neuroprotective characteristics such as antioxidant, antidepressant, anticonvulsant activities (Yeggoni et al. 2015). The ethanolic extract of *Piper longum* fruits exerts anti-snake venom activities as neurotoxins present in the snake venom cause deadly effects on CNS (Vasavirama and Upender 2014). Research studies have also suggested that PIP dramatically reduces memory impairment at all dosage.

Vascular dementia is generally characterized by memory deficits and cognitive impairment that result from cerebrovascular diseases. Some studies have shown that medicinal plants, predominantly Sancaijiangtang and *Ginkgo biloba*, might improve behavioral and psychological symptoms, executive functions, working memory, and overall quality of life in patients with vascular dementia (Ghorani-Azam et al. 2018).

Overall, clinical data on phytochemicals against neurodegenerative diseases are still not adequate. Therefore, additional human prospective studies should be conducted to explore the possibility of using combined therapeutic approach that may provide further insights on the possible treatment of these patients.

2.5 Major Depressive Disorder

Depression is the recurrent, common, and leading risk factor for suicide cases that is attributable to multiple psychological causes. Conventional antidepressant therapy can help in relieving symptoms associated with depression and prevent relapse of the illness. However, most of these antidepressant drugs have undesirable side effects, thus limiting their daily use in curing these patients. Consequently, more specific agents with lesser side effects are necessary as a new therapeutic modality for the rational treatment of depression. One potential complementary method with conventional antidepressants involves the use of medicinal herbs and phytochemicals that provide therapeutic benefits. St. John's wort's (*Hypericum perforatum*) has a 2000-year history of use as a medicinal herb. Its modern application as a plant extract for alleviating the condition of depression has undergone scientific investigation over the last decade, and its effectiveness has been shown in studies comparing it with placebo and reference antidepressants (Vorbach et al. 2000) Therefore, extracts from St. John's wort's are widely used as phytopharmaceutical agents to reduce symptoms in elderly patients with depressive disorder. In a previous study (Oztürk 1997), antidepressant effects of other *Hypericum* species on animal models were also reported. The beneficial effects of medical herbs and phytochemicals on depression and their central nervous system mechanism have been described in many research studies. Based on accessible information (Lee and Bae 2017; Yeung et al. 2018), black cohosh, chamomile, chasteberry, lavender, passionflower, and saffron appear promising in mitigating depression with favorable risk-benefit profiles compared to standard-of-care treatment comprising of synthetic drugs.

Recently, Khan et al. (2018) reported significant medicinal potential and clinical possibility of glycosides as antidepressant agents. Through preclinical tests, it has been observed that efficacy of glycosides is mediated by the modulation of brain-derived neurotrophic factor (BDFN) in the hippocampus, an important brain structure for promoting synaptic efficacy, neuronal connectivity, and neuroplasticity. Thus, any physiological process or molecular pathway that helps to upregulate the expression of BDNF may be a novel therapeutic strategy for the treatment of depression. Several human clinical trials have shown positive antidepressant effects of *Echium amoenum*, *Crocus sativus*, and *Rhodiola rosea* (Sarris et al. 2011). However, a caution should be taken while interpreting these exciting findings as many of these published studies in the literature have not been replicated and reproduced in the subsequent studies. Moreover, therapeutic potential of several herbal medicines still remains unexplored in clinical trials. Thus, future studies are required to explore and confirm the efficacy of medicinal plants in curing patients with depression.

2.6 Bacterial Infections

Pyogenic infectious diseases are a significant cause of morbidity and mortality worldwide, accounting for approximately 50% of all deaths in tropical countries and as much as 20% of deaths in the developed countries. Despite the significant progress made in developing mechanisms to control microbial growth and transmission of infectious diseases, sporadic episodes of epidemics owing to presence of drug-resistant microorganisms and unknown disease-causing pathogens cause a widespread threat to the public health. Over the past several years, the active compounds isolated from medicinal plants have served as structural and functional ingredients for many clinically proven drugs. Numerous plant species have been tested against several bacterial strains, and many medicinal plants are active against a wide range of gram-positive and gram-negative bacteria. Unfortunately, a very few of these medicinal plant extracts have been examined in preclinical or clinical studies to determine their true reliability and degree of effectiveness.

More than half of the world population is infected with *Helicobacter pylori* pathogen. This bacterium causes peptic and duodenal ulcers. Anti-*H. pylori*-induced gastric inflammatory effects of plant products include quercetin, apigenin, carotenoid-rich algae, tea product, garlic extract, apple peel polyphenol, and fingerroot extract (Wang 2014). These purified natural products have anti-H. pylori-induced inflammation activity, and they cause suppression of nuclear factor-κB and mitogen-activated protein kinase pathway activation and inhibition of oxidative stress.

Diarrhea is a common ailment which causes pain and may become lethal if remains untreated, especially in the developing countries. A great number of plant species such as *Diospyros peregrina*, *Heritiera littoralis*, *Ixora coccinea*, *Pongamia pinnata*, *Rhizophora mucronata*, *Xylocarpus granatum*, and *Xylocarpus moluccensis* (Wangensteen et al. 2013) are used in the treatment of diarrhea. Among these compounds, the most promising components are the barks from *D. peregrina*, *X. granatum*, and *X. moluccensis* which contain tannins. These valuable compounds have shown strong results in anti-diarrheal mice models. The leaves of *P. pinnata* also show great potential against diarrhea. However, more work is required to study efficacy, optimal dosage, and safety profiles of these useful compounds in treating patients with diarrhea.

In an earlier study, Ullah et al. (2017) reported positive and beneficial anti-mycobacterial effects of *Citrullus colocynthis*, *Calotropis procera*, *Ricinus communis*, *Capparis decidua*, and *Fagonia cretica* plants' extracts against rifampicin-sensitive (H37Rv) and rifampicin-resistant (TMC331) strains of *Mycobacterium tuberculosis* as possible therapy against tuberculosis. In a seminal work, Komape et al. (2017) stated that plant species *C. lemon*, *C. heroroense*, and *A. dimidiata* possess compounds with antioxidant activity, suggestive of their

significance in the scavenging of free radicals that may accumulate in a disease condition. In that study, all the extracts of plants were tested, and findings established some degree of anti-mycobacterial activity of these individual extracts, and this effect was potentiated when a combination of different extracts were employed suggesting this desired effect was possible because of synergistic interactions among different components. The investigators of this study also reported that hexane and butanol sub-fractions of *A. dimidiata* exhibited potent anti-mycobacterial activity.

In spite of encouraging results, there is a further need for the development of more powerful anti-mycobacterial drugs against multidrug-resistant (MDR) bacteria that are largely responsible for the cases of therapeutic failure. Results obtained from a recent study (Voukeng et al. 2017) highlight the antibacterial potential of the tested plants and the possible use of *Euphorbia prostrata* to combat bacterial infections including MDR phenotypes, thus raising a hope of providing cure to patients infected with MDR bacteria.

There also exists a great variety of plant species whose extracts have shown potential anthelmintic properties. One of the most potent extracts obtained from *Piper chaba* is dichloromethane fruit, that is usually called "Dee Plee" in Thailand and has been used collectively as an antiflatulent expectorant, antitussive, antifungal, uterus-contracting agent, sedative-hypnotic, appetite enhancer, anthelmintic, and counterirritant agent (Tewtrakul et al. 2000). Moreover, the aqueous acetone extract from the fruit of *Piper chaba* has been found to have hepatoprotective effects (Matsuda et al. 2009). Some amides have been isolated from the methanol extract of the *P. chaba* fruit (Morikawa et al. 2009) from the chloroform extract of the *Piper chaba* root. These amides such as Bornyl piperate and piperlonguminine have been found to possess potent antifungal and cytotoxic activities. Bornyl piperate and piperlonguminine demonstrated weak activity against *Leishmania donovani* promastigotes when compared against the standard drug, pentamidine (Tewtrakul et al. 2000). Other potent extracts include hydroalcoholic leaves of *Musa paradisiaca* (banana), which is known to inhibit *H. contortus*. Other activities have been described for the peel or the fruit of *Musa paradisiaca* including anti-leishmaniosis activity, anti-oxidative properties, and antimicrobial properties (Gachet et al. 2010).

In vitro, the anti-leishmanial activities of triterpenes and sterols isolated from *Musa paradisiaca* fruit peel have also been widely studied. The stem and root extracts of *Trianthema portulacastrum* are effective against the eggs of *H. contortus*; the dichloromethane bark of *Michelia champaca* is effective against *S. mansoni*; and the dichloromethane root extract of *Plumbago indica* is useful when tested with *C. elegans*. It is expected that preclinical studies are adequately reliable, and conclusions drawn from these studies are often transferable to clinical settings. Moreover, some studies have reported a significant correlation between in vitro tests and in vivo clinical studies of anthelmintic and parasitic drug resistance. Although studies using animal models are labor-intensive, expensive, time-consuming, and often difficult to scale up, they provide valuable insights into the action mechanisms,

efficacy, and safety profiles of the potential drugs. In line with this argument, some studies (Adamu et al. 2016) are ongoing with the aim of assessing the cytotoxic effects of segments that are responsible for the antimicrobial activities.

2.7 Periodontitis

Periodontal disease has been recognized as a major health problem worldwide. Periodontal disease is an infectious disease caused by bacteria present in dental plaque (Chaturvedi 2009), and there exists a direct relationship between the presence of dental plaque and development of gingivitis (Powell 1965). Periodontitis is a complex disease in which disease expression involves intricate interactions of the biofilm with the host inflammatory response and subsequent modifications in bone and connective tissue metabolism.

Plant extracts and various natural products such as *Curcuma zedoaria*, calendula, *Aloe vera*, and other herbs have been used successfully to treat oral diseases. *A. vera*, star anise oil, myrrh gum, calendula extract, fennel oil, tea tree oil, and neem extract are some of natural products that are used to control periodontal disease (Maxwell 1995). Additionally, *Psidium guajava* is one such plant that has been used to control periodontal health (Ravi and Divyashree 2014). Other examples, *Centella asiatica* and *Punica granatum*, are medicinal plants that have been reported to promote tissue healing and modulate host responses.

It has also been demonstrated that curcumin, a component of turmeric which is used as a dietary spice, exerts a potent anti-inflammatory activity against LPS-induced periodontal disease (Guimarães et al. 2012). Another study (Moradi et al. 2014) suggested that anethole may have a strong inhibitory effect on periodontal disease through suppression of pro-inflammatory molecules. Anethole is a monoterpene and the main component of essential oils from aromatic plants including anise, star-anise, and fennel. An in vitro study showed the antimicrobial activity of lemongrass essential oil against periodontal pathogens, especially the strains *Actinomyces naeslundii* and *Porphyromonas gingivalis*, which were resistant to tetracycline hydrochloride. Lemongrass essential oil in the form of mouthwash was shown to be an effective aide to SRP as a part of nonsurgical therapy for the treatment of gingivitis (Warad et al. 2013). At the end, we would like to emphasize that all these medicinal herbs may be used in conjunction with the scaling and root planning or any other periodontal therapy as recommended by a certified dentist.

2.8 Viral Infections

The viruses cause a large number of human diseases. Currently, viral infections are clinically managed through administration of available antiviral regimens with poor therapeutic outcomes. The recalcitrant viral infections that remain generally resistant to accessible antiviral drugs are serious health concerns. For example, the available

interferon and vaccine therapies for treating viral hepatitis are not definitive solutions due to high mutation and recurrence rates associated with hepatitis C virus. Owing to the growing incidences of viral infections because of globalization and ease of travel, the available therapeutic modalities are not sufficient to treat patients. As a result, there is an urgent need to discover novel antiviral agents to combat refractory viral infections. It is widely accepted that medicinal plants are repository of antiviral metabolites. These medicinal plants preserve a variety of bioactive products that harbor powerful therapeutic index and thus assist in inhibiting viral growth and possible elimination of viruses.

Several studies (Jassim and Naji 2003; Naithani et al. 2008; Ma et al. 2002; Ho et al. 2010) have shown the therapeutic potential of medicinal plants in the eradication and management of various viral diseases such as influenza, human immunodeficiency virus (HIV), herpes simplex virus (HSV), hepatitis, and coxsackievirus infections. These studies have documented several medicinal plants belonging to different families possessing useful antiviral properties. Taken together, *Sambucus nigra*, *Caesalpinia pulcherrima*, and *Hypericum connatum* hold promising specific antiviral activities that have been scientifically tested using experimental animal models. Though most of the clinical trials have reported some benefits from use of antiviral herbal medicines, the adverse effects of these natural products in the clinical trials have not been well documented in the literature (Martin and Ernst 2003). We believe that larger, stringently designed, randomized clinical trials are required to provide definite evidence of efficacy and safety profiles of natural antiviral drugs.

2.9 Current Challenges

Of a large number of flowering plant species identified until the present time, only about 10% of these species have been investigated for deciphering biological activities and that too not systematically. This condition suggests that a vast majority of the phytochemical diversity still requires further exploration. However, there are some stumbling blocks that need to be addressed before basic scientific findings in a laboratory setting could be successfully translated into clinics for potentially treating diseases and life-threatening conditions. The major obstacles that impede the growth of herbal medicine include loss of biodiversity, overexploitation and unscientific usage of medicinal plants, industrialization, and biopiracy, along with absence of regulatory mechanisms.

There also exist some pitfalls that prevent proficient and consummate utilization of phytochemicals in therapeutics. The main challenge is the short bioavailability associated with these phytochemicals. As large number of phytochemicals are readily digested and excreted from our body, they exert a transient therapeutic effect. New technologies and methods such as development of stabilizers and coating or capping of bioactive molecules into microparticles or nanoparticles are required to potentially increase the absorption, biostability, and efficacy of important phytochemicals. Another challenge is the absence of specific target sites for phytochemicals to act. Since phytochemicals have a pleiotropic effect, the neoplastic

cells very frequently initiate different molecular and signaling pathways resulting in the failure of targeted therapies. To address these issues, alternative strategies including novel formulations of targeted delivery of these phytochemicals are being explored.

2.10 Conclusory Remarks

Medicinal plants shape an eco-friendly, bio-friendly, cost-effective, and safe mode of alternate healthcare system. Crude plant extracts encompass a variety of constituents that may employ their therapeutic effects either alone or synergistically if these different components are used together. However, detailed screening of medicinal plants is required for the further detection and progress of novel natural compounds that would help in combating many human diseases.

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