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Luwangshangbam James Singh
Department of Plantation, Spices, Medicinal and Aromatic Crops, Faculty of Horticulture, BCKV, Mohanpur, Nadia, Kolkata, West Bengal, India

Dawan Arkini Challam
Department of Plant Physiology, Faculty of Agriculture, BCKV, Mohanpur, Nadia, Kolkata, West Bengal, India

Bidyarani Devi Senjam
Department of Pomology and Post Harvest Technology, UBKV, Cooch Behar, Kolkata, West Bengal, India

Correspondence:
Luwangshangbam James Singh
Department of Plantation, Spices, Medicinal and Aromatic Crops, Faculty of Horticulture, BCKV, Mohanpur, Nadia, Kolkata, West Bengal, India
Email: luwangjameshort@gmail.com

Medicinal plants as a sources of terpenoids and their impact on Central Nervous System disorders: A review

Luwangshangbam James Singh, Dawan Arkini Challam, Bidyarani Devi Senjam

ABSTRACT

Medicinal plants are rich sources of secondary metabolites which are commonly used in treating and preventing various diseases. Among different secondary metabolites, terpenoids play an important role as signaling compounds and growth regulators in plants. Besides these, terpenoids also have medicinal properties which are effectively used in treating common Central Nervous System disorders such as anti-Parkinson´s disease, anti-Alzheimer's disease, anti-malarial, anti-ulcer, hepaticidal, etc. Terpenoids were also known for their potential role in improving intelligence, memory-enhancing, and exerting antidepressant and antianxiety effects. The availability of medicinal plants in nature is an indication for combating various diseases since synthetic drugs have serious side effects that negatively affect the treatment outcome. Thus, the need to strengthen the research on reservoirs of phytochemicals that are present abundantly in medicinal plants is important for their identification, isolation, and characterization of particular drug-yielding compounds against several diseases. In this review, we have summarised the important potential of medicinal plants' terpenoids and their effects on Central Nervous System disorders.

Keywords: Central Nervous System, Medicinal plants, Phytochemicals, Secondary metabolites, Terpenoids.

INTRODUCTION

Herbal medicines have been used for medicinal purposes since ancient times to treat various human diseases due to its curative properties[1]. Their demand increased significantly due to their beneficial impact on human health. Traditional medicines especially Ayurveda gained a lot of popularity in the 20th century among developed and developing countries as people are more aware of the limitations and adverse effects of modern medicines. According to World Health Organization, around 80% of the world's population is estimated to use traditional medicine, such as herbal medicines, acupuncture, yoga, indigenous therapies, and others. India is having 2.4% of the world's area with 8% of global biodiversity according to International Union for Conservation of Nature and over 70% million of the population still depend on herbal drugs for their health prescribed in the non-allopathic systems of medicine such as Ayurveda, Yoga, Unani, Siddha, Homeopathy, and Naturopathy [2, 3]. Based on Market Research Report Analysis 2022, the global herbal medicine market indicates an increasing growth rate of 8.46% in 2020 compared to growth in 2017-2019, and it is estimated to grow from USD 230.03 billion in 2021 to USD 430.05 billion in 2028 at a Compound Annual Growth Rate (CAGR) of 11.32% in 2021-2028 phase. This increase is majorly due to the increasing demand for herbal and natural ingredients of medicinal plants from various cosmetics, pharmaceuticals, and nutraceuticals industries.

Phytochemicals are biologically active naturally occurring plant-based compounds that have great antioxidant potential and provide immense health benefits for human beings [4]. Modern medicine can cause long term side effects on the human body [5], such unwanted effects can cause minor to severe health issues like diarrhea, headache, nausea, internal bleeding, cancer etc. Hence this necessitated the need for herbal medicine, especially for longer treatment conditions that are safer than synthetic drugs, therefore, natural drugs can be the most relevant alternative source of drugs against neurological disorders. To become a feasible alternative to modern medicine, a vigorous method of clinical evidence must be exercised to prove the safety and effectiveness of pharmaceuticals. Although there is sufficient scientific preclinical evidence available on the impact of medicinal plant species in model systems, however human clinical studies are scarce and methodologically weak with different duration and a limited number of patients. Therefore, it is necessary for the identification, isolation, and characterization of several phytochemicals for treating Central Nervous System disorders.

Medicinal plants contained numerous bioactive phytochemicals that are responsible for healing various illnesses. They are majorly included in Primary and Secondary metabolites.

***Primary metabolites*:** These metabolites perform a physiological function in the organism which is directly involved in normal growth, development, and reproduction. It includes Carbohydrates, Vitamins, Proteins, Enzymes, Lipids, Amino acids, and organic acids. They are commonly used as nutritional supplements or flavouring agents and are hardly used as therapeutic compounds [6].

***Secondary metabolites*:** These metabolites plays an important role in protecting the plants against harmful environmental conditions. It includes alkaloids, flavonoids, glycosides, tannins, saponins, phenolics, and terpenoids. Among the secondary metabolites, terpenes contribute highly to industrial and medicinal applications due to their large availability and diversity [7]. Certain terpenes were widely used in natural folk medicine and traditional Chinese medicine products [8].

***Terpenoids*:** Terpenes constitute the largest group of secondary metabolites which derived from the union of 5-carbon Isoprene unit. Terpenoids are modified class of terpenes that present in all classes of living organisms such as bacteria, fungi, plants, etc. It plays an important role in involving all forms of plant interactions with other organisms including plant reproduction, defence, signaling, and plant growth regulators [9]. Terpenoids have been widely used in most pharmaceutical industries, flavour and aroma chemicals and are also actively being explored as alternatives to petroleum-based products.

***Classification of Terpenoids*:** Terpenoids are majorly classified into Monoterpenoids (C_{10}, 2-isoprene unit), Sesquiterpenoids (C_{15}, 2-isoprene unit), Diterpenoids (C_{20}, 2-isoprene unit), Sesterpenoids (C_{25}, 2-isoprene unit), and Triterpenoids (C_{30}, 2-isoprene unit).

***Monoterpenoids*:** These occurs as an important component of essential oils in many plant species and gives a characteristic odor which has insect repelling properties. Menthol is a chief monoterpene component of peppermint oil. It also acts as a direct stimulus on the cold receptors at the nerve endings which in turn stimulate the Central Nervous System. Linalool and linalool-rich essential oils exhibit various biological activities against some ailments such as antimicrobial, anti-inflammatory, anticancer, and antioxidant properties, and several in vivo studies have claimed that linalool compound has sedative effects on Central Nervous System, including hypnotic, anticonvulsant, and hypothermic properties [10, 11]. Geraniol found in many essential oils of fruits, vegetables, and herbs has a wide spectrum of pharmacological activities such as antimicrobial, anti-inflammatory, antioxidant, anti-cancer, and neuroprotective, it has also been shown to sensitize tumour cells in chemotherapy agents that represents a promising cancer chemo-preventative compound [12].

***Sesquiterpenoids*:** These are the largest group of isoprenoids which have great structural variations and are found in plants and insects, as semi-chemicals, like defensive agents or pheromones. Artemisinin a popular sesquiterpene derived from *Artemisia annua* has been developed into a potent antimalaria drug called artesunate, which is used against the deadly *Plasmodium falciparum* [13, 14, 15]. Bilobalide from *Ginkgo biloba* is an antagonist potency at recombinant human a1h2g2L G-aminobutyric acid $GABA_A$ receptors that enhanced neuronal excitability in hippocampal slices [16]. *Ginkgo biloba* extract (EGb 761) appears to be more effective in the treatment of dementia irrespective of the severity of neuropsychiatric symptoms [17]. Sesquiterpenoids compound extracts from *Tussilago farfara* have beneficial therapeutic potential for the treatment of neurodegenerative diseases through inhibition of microglial activation [18]. *Matricaria chamomilla* inhibits the reactivity of the hypothalamus and pituitary system in rodents and can suppress the reactivity of the Central Nervous System [19, 20]. The neuroprotective effect of farnesol has been reported in lipopolysaccharide induced-neurodegeneration of the cortex and hippocampus of Swiss Albino mice [21].

***Diterpenoids*:** These are the basic form of biologically important compounds such as retinol, retinal, and phytol and are known to be antimicrobial and anti-inflammatory properties [22, 23]. Taxol, a tubulin binding diterpene is an anticancer drug from *Taxus brevifolia* was first reported by Wani *et al.* [24]. Taxol was also produced at low levels by endophytic fungus *Taxomyces andreanae* [25, 26]. Andrographolide obtained from *Andragraphis paniculata* has been reported to have neuroprotective effects against cerebral ischaemia [27]. Ginkgolide B isolated from the leaves of *Ginkgo biloba* was found to effectively reduces Intracranial pressure and increase Cerebral perfusion pressure which benefit brain metabolism [28]. Forskolin obtained from *Plectranthus barbatus* act as psychostimulant effects and can perceive increased energy levels which improves mental alertness [29].

***Sesterterpenoids*:** These compounds are naturally present in marine organism, lichens, fungus, sponges, insects, etc and hence, are not considered as a source of herbal medicine.

***Triterpenoids*:** These terpenes play a potential role in plant defense and development. Glycyrrhizin a flavonoid glycoside extracted from *Glycyrrhiza uralensis* promotes sciatic nerve regeneration by inhibiting p75 neurotrophin receptor (p75NTR) expression at the protein and mRNA levels [30]. *Glycyrrhiza glabra* extract may be used in neurologic improvement of patients with acute ischemic stroke [31]. Digitoxin from *Digitalis purpurea* has been used to treat heart conditions since the 12th century and considered one of the safest and most effective compound on the list of essential medicines by World Health Organization's. It is a promising anti-cancer drug, considering the molecular modes of actions and pharmacokinetics; glioblastoma, pancreatic cancer, leukaemia, kidney cancer, urothelial carcinoma, and cholangiocarcinoma[32]. Bacoside A from *Bacopa monnieri* has protective role against morphine induced brain oxidative damage in the antioxidants and membrane-bound ATPases activities in the rat [33].

***Central Nervous System disorders*:** Any disorder that can affect the structural, biochemical and functions of the brain and spinal cord, resulting in neurodegenerative complications. Neurological disorders are defect of the central and peripheral nervous systems which includes dementia, epilepsy, bipolar disorder, multiple sclerosis, neuro infectious. It is also associated with malnutrition, pain, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, cerebral ischemia, traumatic brain injuries, *etc.* [34]. Alzheimer's disease is the most common cause of dementia and contributes to 60-70% of neurological cases [35]. Synthetic drugs are commonly used in the treatment of such neurological disorders. However, there is an inefficient lack of drugs for long-term use and their high cost are some of the major concerns for millions of affected populations. Apart from synthetic drugs, some plant species have been reported in therapeutics that are used to treat human ailments as traditional medicine [36]. So, there is a potential and possibility to use plant-based drugs as an alternative to synthetic drugs in the treatment of neurological disorders. Therefore, some of the collective information and research studies have been reviewed and draw attention to medicinal plants species having positive effects on Central Nervous System disorders are discussed here:

Effect of medicinal plants' terpenoid on Neuroprotective functions

Neuroprotection refers to the mechanisms and strategies employed to defend the Central Nervous System against injury due to both acute and chronic neurodegenerative disorders [37]. Common neuroprotective treatments are glutamate antagonists and antioxidants properties, which aim to limit excitotoxicity and oxidative stress respectively. Herbal medicine and nutraceuticals represent an important and valuable source in prevention rather than treatment of neurological disorders [38]. *Centella asiatica* is a promising treatment for Alzheimer's disease as it prevents colchicine-induced cognitive impairment and associated oxidative damage [39]. Asiatic acid isolated from *Centella asiatica* acts as a protective agent against amyloid-β (Aβ) formation and neuroinflammation [40]. Andrographolide from *Andrographis paniculate* has been reported to reduce cerebral infarct volume in suppressing neuroinflammatory and synaptic dysfunction in Alzheimer's disease models. Further, andrographolide has been shown to inhibit chronic stress-induced abnormalities in serum corticosterone levels, mood-associated behaviour, and hippocampal neurogenesis, suggesting that andrographolide may have the potential to treat psychiatric disorders, such as anxiety and depression [41]. In a clinical study, andrographolide was reported to provides neuroprotection against ischaemic injuries in the brain [42]. *Pinus densiflora* and *Vitis vinifera* extracts have neuroprotective effects against ischemic insults in both *in vitro* and *in vivo* cerebral ischemia models [43]. The terpenoids compound 20-hudroxy-3-oxolup-28-oic acid extracted from *Viburnum odoratissimum* has neuroprotective effects on human dopaminergic neuroblastoma cells and might be useful for the treatment of neurodegenerative diseases [44]. Methanolic compound extracts from *Acalypha alnifolia, Pavetta indica,* and *Ochna obtusata* may act as a great natural source for the establishment of new agents in combating age-related neurodegenerative diseases like diabetes mellitus and Alzheimer's disease [45]. Ginkgolide B and *Ginkgo biloba* extracts have been suggested to have a multitude of beneficial effects on Central Nervous System [46]. The presence of dopamine precursor in *Portulaca oleracea* is considered as a therapeutic potential for treating neurodegenerative diseases in rat models of Parkinson's disease [47]. Ethanol extract of *Portulaca oleracea* L. also has neuroprotective effects against hypoxia injury [48] and D-galactose-induced toxicity *in vivo* [49].

Stimulant effects of medicinal plants' terpenoid on Central Nervous System

Stimulants are a class of drugs that increases levels of certain chemicals between the brain and the body such as alertness, attention etc. A preliminary study shows that methanolic extract and ethyl acetate fraction from *Alpinia galanga* rhizome enhances the stimulation of Central Nervous System in swiss albino mice [50]. Caffeine from *Coffea arabica/robusta* induce temporary improvements in mental and physical function by enhancing the Central Nervous System [51]. Leaves extract of *Centella asiatica* is reported to have Central Nervous System effects such as nerve tonic, rejuvenate, sedative, and tranquilizer effects and is reputed to increase intelligence and memory [52]. *Centella asiatica* extracts also improve learning and memory ability in mice [53]. In pharmacological and clinical trials, *Centella asiatica* has been found to improve the power of concentration, general ability and behaviour of mentally retarded children [54]. *Bacopa monnieri* can improve attention, cognitive processing, and working memory partly via the suppression of plasma Acetylcholinesterase activity [55] hence, its consumption can enhance memory recall [56, 57]. *Withania somnifera* stimulates the growth of axons and dendrites in human neuroblastoma cells and rat neurons [58, 59] and it also enhances cognition and improves memory effects [60, 61].

Anticonvulsant potentials of terpenoids from medicinal plants

Anticonvulsants are also known as antiepileptic or antiseizure drugs which are used in treatment of epileptic seizures that occur due to excessive, abnormally synchronized, localized, or widely distributed neuronal electrical discharges [62]. These seizures are considered one of the most serious chronic neurological conditions at any age affecting around 60 million people worldwide [63, 64]. Most of the available anticonvulsant drugs are synthetic drugs with limited supply, high cost as well as low efficacy with adverse side effects. Hence, medicinal plants were used as an alternate to this remedy [65]. Several animal models have been conducted in the search for more efficacious and more tolerable antiepileptic drugs. The previous study revealed that extracts of *Centella asiatica* can be used to treat epilepsy in animal models [66, 67]. Bilobalide, a sesquiterpene constituent of the *Ginkgo biloba* extract was found to exert anticonvulsant activity as bilobalide hinders Ginkgotoxin (4-O-methylpyridoxin) in reducing the Gamma-aminobutyric acid levels by protecting glutamic acid decarboxylase activity [68].

Anti-anxiety and anti-depressant potentials of terpenoids from medicinal plants

Anxiety is a disorder and group of mental illnesses caused by behavioural disturbances. Whereas depression is a serious clinical disorder that is associated with symptoms of major depression are disturbances in mood and anhedonia. Anxiety and depression are affecting a wide range of the general population and public health conditions, and account for multibillion-dollar expenditures directly related to health care and hospitalizations and indirectly related to morbidity and mortality [69, 70]. The mechanism causes of such disorders are not clear. However current evidence suggested that the neurobiological mechanism of anxiety was related to dysregulation of serotonergic, noradrenergic, glutamatergic, and Gamma-aminobutyric acidergic transmission [71]. Several herbs show similar effects like chemical drugs that manage to relieve anxiety and depressions. Some antidepressant drugs prescribed by doctors are obtained from herbs through various extracts. Studies revealed that the terpenes formed a major part of the extracts of medicinal plants that exerted antidepressant effects [72]. Present studies show the action of various herbal mechanism used in therapy of depression, anxiety, insomnia etc. However, a systematic review of herbal pharmacology in depression, anxiety, and insomnia is still scarce. Therefore, some of the studies have been performed and stated that some plants have a potential effect against such disorders are detailed here; The anxiolytic activity of preclinical evidence was found in 32 plants and human clinical trials evidence from 21 plants [73]. Extracts from *Centalla asiatica* and Valerian and valerenic acid from *Valeriana officinalis* produce anxiolytic and sedative effects [74]. *Matricaria recutita* and *Humulus lupulus* inhibited the enzymatic activity of Glutamic acid decarboxylase. Aqueous extract of *Melissa officinalis* was found to have the largest inhibitory activity of Gamma-aminobutyric acid Transaminase [75]. Bilobalide from *Ginkgo biloba* indicated its cognitive enhancing activity in Ts65Dn mice [76]. *Lippia genus* extracts can relieve anxiety and act as an adjuvant in seizures treatment of epileptic patients, as well as an analgesic activity [77]. *Lippia graveolens* exerts anxiolytic-like activity in nature which

reinforces the potential use of this species in the therapy of anxiety [78]. Thymol produced a significant anti-anxiety effect on mice in both elevated plus maze and the light/dark test behavioral models [79, 80]. The methanol extract of *Trachyspermum ammi* L., revealed anxiolytic activity may be due to the presence of high thymol contents [81]. A large number of experimental studies on plant extracts such as *Withania somnifera* [82], *Ocimum sanctum* [83], and *Camellia sinensis* [84], *Withania somnifera* [85] have been demonstrated to be effective as anti-stress agents. Similar to other antidepressants compound, hyperforin extracts from *Hypericum perforatum* acts an antidepressant agent by inhibiting the neurotransmitters Gamma-aminobutyric acid and l-glutamate uptake [86]. As details of the given review on the preclinical evidence of plant-based anxiolytics provide an area of potential future interest.

Anti-malarial activity of terpenoids from medicinal plants

Malaria is an infectious disease caused by *Plasmodium spp*. that affects humans and other animals. Human malaria is caused by *P. falciparum, P. vivax, P. ovale, P. malariae, P. knowlesi* and *P. simium*, where the last one is exclusive to the Brazilian Atlantic Forest [87]. According to the World Health Organization report on 2020, malaria cases increased globally by one million in 2019 as compared to 2018 and India constitutes 77% of the total cases in Southeast Asia. Malaria can cause a severe neurological syndrome termed Cerebral Malaria that affects the brain and mental state of the infected organism. It is one of the most common and potentially life-threatening neurological complications associated with severe falciparum malaria. Recent studies showed that terpenoid compounds from different plant species have anti-malarial properties. *Clerodane*, a diterpenes compound from ethanolic extract of *Polyanthia longifolium* var. pendula, is traditionally used to treat malaria patients in Ghana [88]. Mellerin B from *Neoboutonia macrocalyx* inhibited the Colombia strain of *Plasmodium falciparum* and it has been reported to use in the traditional treatment of malaria [89]. The extracts of *Erythrina schliebenii, Holarrhena pubescens, Dissotis melleri* and *Caesalpinia bonducella* exhibited antiplasmodial activity against *P. falciparum* (Dd2) parasites [90]. The novel sesquiterpenoids salaterpenes A-D, and 2β-acetoxy-1α,6β,9βtribenzoyloxy-4β-hydroxy-dihydro-β-agarofuran isolated from the seeds of *Salacia longipes* exhibit anti-malarial properties which inhibited the W2 strain of *P. falciparum* [91]. Another sesquiterpene sclerienone C from the rhizomes of *Scleria striatonux* also exhibited antimicrobial and antiplasmodial activities [92]. Ganoderic acid AW1, a lanostane triterpene from *Ganoderma* spp. shows good anti-malarial activity against the D6 and W2 strains of *P. falciparum* [93]. Cryptobeilic acids A - D, and tsangibeilin B exhibited anti-plasmodial activity against erythrocytic stages of chloroquine-resistant *P. falciparum* strain NF54 [94]. The antiplasmodial activity of these extracts from different plant species and identification of isolated bioactive compounds indicates that they may play an important role in pharmacological properties and potential for new drugs against malaria.

CONCLUSION

Medicinal properties herbs are the reservoirs of potential drugs due to the presence of secondary metabolites, especially terpenoids compound. Such herbal medicines play a vital role in the treatment of many diseases. Thus, the only solution against the side effects of modern medication is through the use of natural plant-based medication which is a nontoxic alternative medicines, socially desirable, economically affordable, and sustainable, delaying or preventing complications of neurological disorders. However, a greater number of true potential drugs are yet to be exploited and readily applicable and available for the treatment of various diseases and further investigation and exploration are necessary to focus on rigorous human clinical trials and a potential application for treating a various Central Nervous System disorders.

Conflict of interest

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ORCID ID

Luwangshangbam James Singh: https://orcid.org/0000-0002-0430-3944

Dawan Arkini Challam: https://orcid.org/0009-0002-5728-2670

Bidyarani Devi Senjam: https://orcid.org/0000-0002-7737-6028

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