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Neuroactive drugs–A perspective on drugs of synthetic and medicinal plants origin

Abstract

There is a gap between traditional knowledge, experimental proof and translational research into clinical studies for acceptance of traditional medicine. They are restricted by the quality of trials, flaws in study design and other important criteria that may affect their success as a clinically accepted drug. This article provides a summary of potential medicinal plants that can be used as natural psychotropic agents based on their fundamental scientific findings. Several reviews have been published that focus on a particular plant or particular neuronal disorder. This article focuses on providing a comprehensive review of different kinds of neuronal diseases, the shortcomings of psychotropic western medicine, the status of medicinal plants and their mechanism of action in various neuronal diseases. The article aims to emphasize establishing collaborative and concerted efforts between the ethnopharmacologists and western medicine practitioners to further provide scientific validation of traditional medicines.

Keywords: medicinal plants, neurological disorders

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Introduction

Neurological disorders

Neurological disorders, specifically Alzheimer's (AD), Parkinson's (PD), depression, anxiety, and cognitive disorders, are indicated to have an increasing trend in their prevalence around the globe.[1–4] According to the World Health Organization (WHO), more than 50 million people have epilepsy and about 35.6 million people are affected by AD or dementia globally.[5] The increase in the prevalence of these conditions is likely due to the increase in life expectancy of people, as most neurological disorders are associated with old age or the impact of living a highly stressful life. Stress factors may be either oxidative or mechanical (trauma), or both and can cause functional changes in the brain that are associated with various brain disorders.[6] Neurological disorders are divided into a number of categories such as neurodegenerative disorders (AD and PD), seizure disorders (epilepsy), mood disorders (anxiety and depression), genetic disorders (Huntington disease and Schizophrenia) and others (addiction, eating disorder, etc). AD and PD are disorders caused by the degeneration of neurons in different parts of the brain. Both these disorders are associated with age, where the build-up of beta-amyloid and tau protein (AD) or Lewy bodies (PD) over time, causes neuronal cell death.[7,8] The AD is the most common type of dementia and AD patients suffer progressive functional impairment, cognitive decline (memory loss), loss of independence, emotional distress and behavioral symptoms.[8] Similarly, PD patients also suffer from progressive functional impairment of motor neurons (tremors), emotional distress and autonomic symptoms.[7]

Unlike AD and PD, epilepsy is a disorder characterized by chronic unprovoked recurrent seizures that occur due to a sudden outburst of intense electrical impulses in the brain.[9] Epilepsy is not governed by age or gender and can be brought on by traumatic injuries to the brain, infection, brain tumor, or congenital complications.[7] Schizophrenia, on the other hand, is a common genetic mental disorder. A combination of genetic and environmental factors are known to contribute to the onset of schizophrenia.[10,11] Depression is a serious long-term or recurrent mental illness that causes one to feel sad, guilty, tired, have low self-worth, and to lose the sense of pleasure.[10] Anxiety disorders can be further classified into various types such as generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), social anxiety disorder, specific phobias, and other less common types.

Synthetic Psychotropic drugs and their shortcomings

Psychotropic drugs can be classified as anti-psychotic, anti-anxiety, antidepressants, psychomotor stimulants, psychotogenic drugs, and other miscellaneous categories. Various drug classes are used to treat different stages of any mental disorder, curb the probability of major side effects, and to account for the variability of drug pharmacology in different people. Psychotropic drugs have side effects after prolonged use, and adversely affect other systems of the body in addition to their central effects. Representative examples of each class of psychotropic drugs, and their central effects and side effects are presented in Table 1. Among the anti-depressant drug classes, selective serotonin reuptake inhibitors (SSRI) such as sertraline are the most commonly prescribed, due to reduced side effects compared to the other drugs in this class.[35]

SSRI and serotonin-norepinephrine reuptake inhibitors (SNRI) are second generation drugs and were developed to have less adverse effects than first-generation drugs such as tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (MAOI).[35,36] Nevertheless, first generation anti-depressants are prescribed to patients who do not tolerate or respond to second generation anti-depressants. In some occurrences, patients are also prescribed with a combination of anti-depressant to increase effectiveness, but this poses the patients to the risk of drug-drug interactions and the resulting side effects.[37,38] Antidepressant drugs even after discontinuation have serious side effects in some patients and these side effects are specific to the class of drugs used.[39]

Table 1 Central effects and side effects of drugs from different drug classes

Drug class	Example of drugs	Central effects		Side effects	
		Effect	**Receptors**	**Effect**	**Receptors**
Anti-psychotic	Risperidone	Reduced positive and negative symptoms of psychosis.[12,13]	Combination of antagonism at D2 receptors and 5HT2A/2C receptors.[12,13]	Weight gain	H1 histamine receptors&serotonin5-HT2C receptor antagonist.[8,15]
			Blocks serotonin receptors (5HT2) more strongly than Dopamine (D2) receptors.[12,13]	Moderate extrapyramidal symptoms (eg: dystonia, akathisia, parkinsonism)	Antagonizing actions on dopamine D2 receptors.[16,17]
			Antagonism at alpha α1 adrenergic receptors.[14]	Hyperprolactinemia	
				Orthostatic hypotension	Antagonizing actions on alpha α1 adrenergic receptors.[18]
				Sedation	Antagonist of H1 receptors.[17]
				Reduction in vigilance	
Anti-anxiety	Duloxetine	Improved mood, sleep, appetite, and energy level, and decrease nervousness.[19,20]	The primary effect of potentiating serotonergic and noradrenergic activity in the CNS.[20]	Sexual dysfunction (eg: loss of libido, anorgasmia)	Potent selective inhibition of reuptake of serotonin and norepinephrine and a weak inhibitor of dopamine transporters.[20]
		Restore the balance of serotonin and norepinephrine in the brain.		Nausea	
				Dizziness	
				Insomnia	
Anti-depressants	Sertraline	Increased mood and decreased feelings of anxiety.[21,22]	Selectively inhibits serotonin neuronal reuptake.[21,24]	Gastrointestinal disturbances	Potent selective inhibitor of neuronal serotonin reuptake and weak effects on both norepinephrine and dopamine neuronal reuptake.[21,22,24,25]
		Reduces premature ejaculation		Nausea	
		Controls vascular headaches.[21,23]		Sexual Dysfunction	
				Weight gain	
				Sleep disturbances	
				Dry mouth	

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Table Continued....

Drug class	Example of drugs	Central effects		Side effects	
		Effect	**Receptors**	**Effect**	**Receptors**
Psychomotor stimulants	Dextroamphetamine	Increases neurotransmitter activity.[26]	Enhances dopamine neurotransmission in the mesocorticolimbic projection and norepinephrine neurotransmission in the locus coeruleus and prefrontal cortex.[27]	Abnormal heartbeat	Stimulates the medullary respiratory centers thus producing faster and deeper breaths.[30]
		Improves cognition (including working & episodic memory).[27]		Hypotension/ Hypertension.	
		Improves stamina &endurance.[28]	Indirect activation of both dopamine receptor D1 and adrenoceptor A2 in the prefrontal cortex.[29]	Loss of appetite	Increased dopamine levels.[30]
				Muscle pain	
				Urinary retention/Painful urinary	Triggers contraction in the urinary bladder sphincter (muscle responsible for controlling urination).[30]
Psychotogenic	Morphine	Provide an analgesia and sedation effect.[31]	Binds to and activates the μ-opioid receptors in the central nervous system.[31]	Respiratory depression	Acts directly and causes reduced responsiveness of the brain stem respiratory centers.[33]
		Depression of cough reflex.[32]	Acts directly on the cough center in the medulla.[32]	Constipation	Reduces gut motility by acting on the myenteric plexus in the intestinal tract.[34]
				Orthostatic hypotension	Triggers peripheral vasodilation.[31]

Anti-psychotic drugs (also known as major tranquilizers and neuroleptics) are primarily used in relieving symptoms of psychosis which are characteristic in certain mental health conditions like schizophrenia and bipolar disorder.[40] Psychosis occurs due to the over-activity of the neurotransmitter, dopamine. It plays a vital role in memory, cognition, and is also relatively involved in controlling voluntary actions. Like drugs of other classes, anti-psychotics drugs also have major side effects. However, evidence suggests that some of the atypical drugs have milder movement-related side effects than the typical drugs.[41–44] For example (as mentioned in Table 1), Risperidone is a newer "atypical" neuroleptic and it is more selective in action as compared to its counter partners, the "typical" neuroleptics.[12–14] The atypical antipsychotics have little or no affinity for D1 receptors, thus they do not have the same side effects as observed with D1 antagonism, that the older first-generation antipsychotics exhibit.[14,17,18] Regardless of the drug category used, the additional factors that alter the intensity of the side effects of drugs are the patient's tolerability, susceptibility to the type of drug as well as the severity of the disorder being treated. Currently, most studies focus on synthetic drugs as treatment options for mental disorders, however, there are many populations with inadequate access to these treatments.[45] In these populations, traditional and herbal treatments are only available options, and therefore we wish to examine these in our article.[45]

Neuroactive medicinal plants and their pre-clinical testing

Formulations from Traditional systems of medicine have been used for centuries globally, despite the increased acceptance of western medicine in therapy. The continued use of traditional medicine and their demand outweighs the benefit to risk ratio consideration by patients. There are several medicinal plants which have been used by traditional medicine practitioners to treat various neurological disorders. Based on a literature survey of neuroactive medicinal plants, a list of medicinal plant varieties and their pre-clinical evaluation data is provided in Table 2. Curcumin, a potent active compound found in turmeric, acts as an anti-inflammatory compound by inhibiting pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) that can be generated by neurodegenerative diseases.[67] *Gotu Kola*, also known as an Indian penny-wort, has been traditionally used as a brain tonic in Ayurvedic medicine for decades. *Hyperricumperforatum* is used to treat mild to moderate depression and *Bacopamonniera* is used as an anxiolytic agent.[68,69] Oxidative stress and mitochondrial failure will eventually lead to the development of AD. Preclinical studies have shown that *Gingko Biloba* extracts have antioxidant properties which reduce oxidative stress and improve mitochondrial respiration and therefore may be useful in preventing or slowing down the progression of the

AD (2015). Ginsenoside isolated from ginseng extracts have reported having properties of preventing neuronal damage caused due to beta-amyloid-induced neurotoxicity and therefore is considered to be a potential agent in the treatment of AD.[70] All these examples demonstrate the importance and long-standing role of various natural products in treating numerous mental disorders.

Table 2 A collection of animal studies of medicinal plants in neurological disorder and their scientific data

Plant	Animals	Dose	Obtained pharmacological effect	Potential compound(s) responsible
Hypericum perforatum	Normal male CD rats	0.3-480mg/kg	Showed antidepressant activity in FST	Hyperoside, isoquercitrin, miquelianin, aglycone quercetin.[46]
Salvia elegans	Normal male ICR mice	25-2000mg/kg	Showed antidepressant activities in EPM, L-DT, FST, and OFT.[47]	-
Ginkgo biloba	Normal male CD rats	5, 10 and 50mg/kg	Showed antidepressant activities in FST and TST	Composition: 8.2% quercetin glycosides, 6.4% kaempferol glycosides, 1.6% methylmyricetin glycosides, 2.98% bilobalide, 1.59% ginkgolide A, 1.16% ginkgolide B and 0.75% ginkgolide C.[48]
Crocus sativus L.	Normal Male ICR mice	150, 300 and 600mg/kg	Showed antidepressant activities in FST and TST	Hexadecanoic acid, crocin 1.[49]
Morinda officinalis	Male Kuming mice and male Wistar rats (DRL72-s schedule)	12.5, 25, 50, 100 and 200mg/kg	Showed antidepressant activity in FST.[50]	-
Centella asiatica L	Normal male Sprague Dawley Rats with olfactory bulbectomy	3, 10, 30mg/kg	Showed antidepressant activities in OFT and EPM.[51]	-
Piper laetispicum	Normal KM male Mice	30, 60, 120mg/kg	Showed antidepressant activities in OFT and FST	Laetispicine and Leatispiamide A.[52]
Curcuma longa	Normal Male ICR Mice	140, 280, 560mg/kg	Showed antidepressant activities in TST, FST and MAO inhibition in the brain.[53]	-
Bacopa monniera	Charles-Foster albino rats	20, 40 mg/kg	Showed antidepressant activities in FST and LHM	Bacoside A[54]
Withania somnifera	Charles Foster male rats	20, 50mg/kg	Showed antidepressant activities in FST and LHT. Lowered endocoid marker, tribulin.	Glycowithanolides[55]
Panax notoginseng	Male KM mice and male SD rats	10, 30, 100, 300, 1000mg/kg	Showed antidepressant activities in FST. Increases levels of 5-HT, Dopamine, and noradrenaline. Lowered intracellular Ca2+	Ginsenosides, Notoginsenosides, gypenosides.[56]
Areca catechu	Male Wistar Rats	4, 10, 13, 50, 80, 100mg/kg (Extract) 2.5, 4, 5, 10, 13, 16mg/kg (Clorgyline)	Showed antidepressant activities in FST, TST	Clorgyline[57]
Bupleuri radix	Male Sprague-Dawley rats. In-vitro culture of SH-SY5Y cell line.	600 and 900mg/kg 10, 100, 1000µg/ml	Showed antidepressant activity in FST. Increased CREB phosphorylation and BDNF levels.[58]	-
Hemerocallis citrina	Male ICR mice	90, 180, 360mg/kg	Showed antidepressant activities in FST, TST[59]	-
Byrsonima crassifolia	ICR albino mice	500mg/kg	Showed antidepressant activity in FST	Rutin, quercetin, hesperidin[60]
Passiflora edulis	Male and Female ICR mice	384, 452, 1920, 2260mg/kg (Extract) 50mg/kg (compounds)	Showed antidepressant activities in TST, FST	Cyclo passifloic acid IX, Cyclopassifloic acid XI[61]
Ceratonia siliqua	Male Albino Mice	25, 50mg/kg	Showed antidepressant activities in FST, TST, might act through adrenergic (α1-adrenoceptors) and dopaminergic (dopamine D2 receptors)[62]	-

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Table Continued....

Plant	Animals	Dose	Obtained pharmacological effect	Potential compound(s) responsible
Hypericum montbretti	Male Swiss albino mice	100, 250mg/kg	Showed antidepressant activities in TST, FST	Rutin, Quercitrin[63]
Tagetes lucida	Male Wistar rats	100-1000mg/kg	Showed antidepressant activity in FST[64]	-
Glycyrrhiza uralensis	Male Sprague-Dawley rats	10, 20, 40mg/kg	Showed antidepressant activities in FST, increased sucrose consumption, might act through antioxidant pathways as an observed increase of SOD activity, inhibition of lipid peroxidation and lessen the production of MDA	Liquiritin[65]
Alchornea cordifolia	Swiss albino mice either sex	50, 100, 200, 400mg/kg	Showed antidepressant activity in FST[66]	-

Passiflora (passion flower extract) and valerian are two well studied medicinal plants and a number of preclinical and clinical studies demonstrate the effectiveness of these two herbs in treating anxiety, depression and sleep disorders.[62,70] Many polyherbal formulations available commercially or in clinical phases for treating anxiety contain passiflora and valerian as their active component.[61,63,64,71–73] Various *in-vivo* models used for the study of the activity of medicinal plants in the treatment of neurological disorders mentioned in Table 2. It is found that most of the medicinal plants found to be active in animal models have flavonoids (quercetin, iso-quercitin, catechin, rutin, hesperidin), terpenoids (ginkgolide A, ginkgolide B and ginkgolide C, hederagenin, Podoandin), amide alkaloids (Leatispiamide A), saponins (Bacoside A), phytosterols (stigmasterol), coumarins (Scopoletin), opioid (Mitragynine) and other constituents as active agents (Figure 1). There are several widely accepted and established animal models of experiments being used for *in-vivo* evaluation for many mental disorders.[74,75] For example, learning and memory models such as radial arm maze, Morris water maze, and y-maze are used to evaluate the effect of medicinal plant extracts in Alzheimer's disease in rats. The basis of learning and memory animal models is to determine how a normal or treated, and damaged or untreated brain processes and retains information when confronted with the psychological nature of a certain task.[76] For mood disorders due to anxiety, elevated plus maze is a commonly used model while tail suspension test and forced swim test is used for depression studies. Depression experimental models are designed based on a concept known as "searching-waiting strategy".[77] Theoretically, in these, the tests, a normal animal subjected to an aversive situation alternates between two kinds of behavior, agitation, and immobility. These can be named as searching-behavior characterized by intense motor activity and expense of energy, and as waiting-behavior characterized by immobility and energy saving. The choice sequences between these kinds of behavior can be named as the searching-waiting strategy.

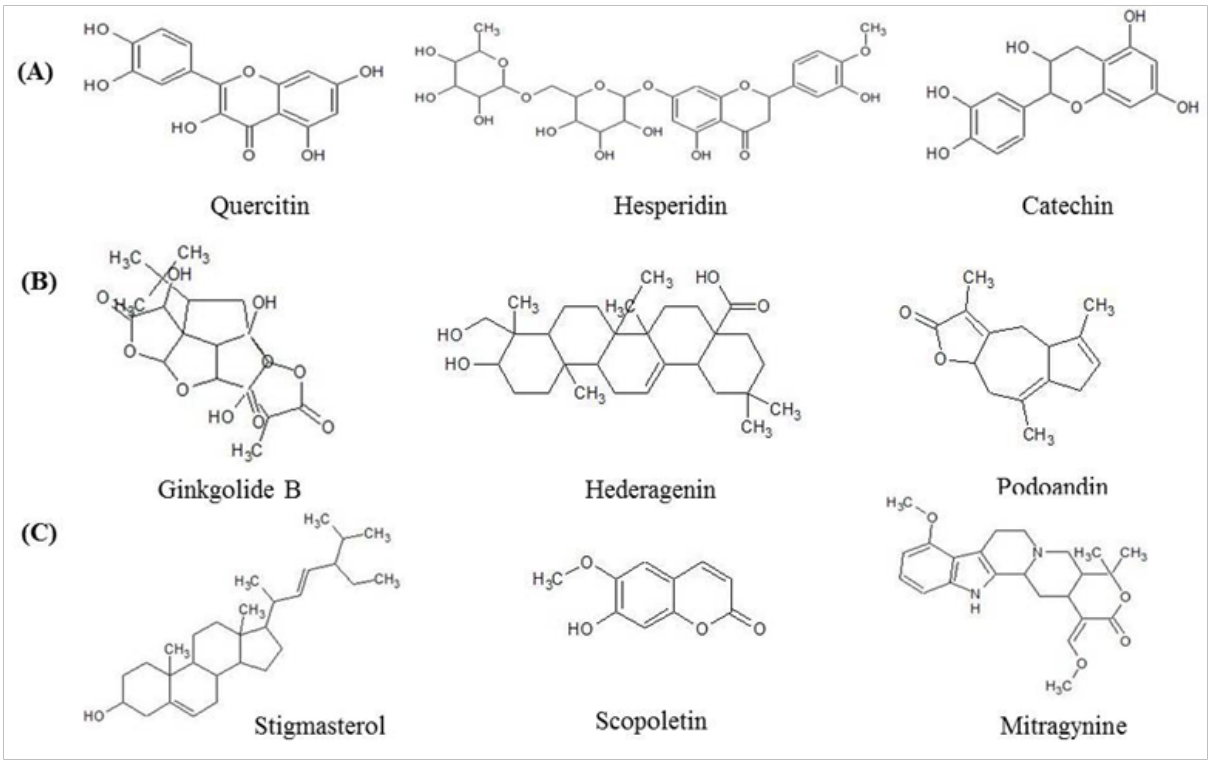

Figure 1 Phytoconstituents reported in neuroactive medicinal plants.

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Mechanism of action of neuroactive medicinal plants

Medicinal plants have been studied in various *in-vivo* and *in-vitro* models and have been reported to have their effects through various pathways in different neuronal disorders. It is difficult to identify the exact phytoconstituents and the mechanism of responsible for any pharmacological effect of plant-based products. Mechanism of action is reported or suggested only by few extensive studies.

Depression and anxiety: Most plants with anti-depressant and anti-anxiolytic effect are reported to show activity in mild to moderate conditions. Plants that exhibited anxiolytic activity are suggested to possess such effect due to binding of their active phytoconstituents to cholecystokinin (CCK) receptors which are known to affect the pathophysiological processes of fear and anxiety.[78] Benzodiazepine receptor (alpha subunit) binding effect has been reported from guinea pig brains in plants with anxiolytic effect.[79] Anti-anxiety extracts are reported to have an effect on the Gamma Amino Butyric Acid (GABA) receptors, the voltage-gated channels and ionic transmission in the brain. Increased GABA neurotransmission leads to a calming effect in patients. Plants are reported to have not only a GABAnergic effect but also serotonergic and dopaminergic activities.[80]

Obsessive-compulsive disorder (OCD): Some plants are reported to have beneficial effects in the treatment of OCD in in-vivo models and it is postulated that the plant extracts exhibit this activity through serotonin reuptake inhibitors or due to blockage of serotonergic neurotransmission, specifically the 5-hydroxytryptamine receptors (5-HT) receptors.[81,82]

Cognition, sleep disorders and Alzheimer's disease: Plant extracts are reported to exhibit properties of improving cognition through their anti-oxidant properties. It is hypothesized that neuronal protection is offered through anti-oxidant activity and this prevents neuronal cell death caused due to excessive exposure to glutamate. Anti-oxidant properties also lead to reduced beta-amyloid toxicity which makes such plants as good candidates for the treatment of Alzheimer's disease.[83,84] Some plant extracts are proposed to have memory enhancing and anti-anxiety effect due to their ability to bind to cholecystokinin receptors (CCKB) which bind to the hormone cholecystokinin (CCK).[85]

Schizophrenia: Phytoconstituents liked cannabidiol (CBD) are reported to be effective in the treatment of psychosis or Schizophrenia. It is hypothesized that CBD has the potential to activate the 5-HT receptor and transient receptor potential cation channel subfamily V member 1 (TrpV1). CBD also restricts the degradation of anandamide (AEA) and facilitates the blockage of G protein-coupled receptor 55. These activities lead to the probable anti-psychotic effect of plants effective in the treatment of Schizophrenia.[86,87]

Parkinson's disease: In animal studies, some plant extracts lead to decrease in apoptosis and reduced neuronal damage caused due to their interaction with Mitogen-activated protein kinases (MAPK), Phosphatidylinositol 3-kinase (PI3K/Akt) and protein kinase C.[88] Phytoconstituents such as ginsenosides exhibit potential to inhibit dopamine uptake and act as NMDA antagonists. This protects neurons from the increase in glutamate levels and dysfunction of the mitochondria.[28,89]

Challenges for acceptance of medicinal plants

A number of drugs in use today are from plant sources and since the last several decades, herbal medicines have made their place in major pharmacopeias of various traditional systems of medicine, across the globe.[90] A substantial amount of pre-clinical studies carried out under strict scrutiny of the concerned animal ethics committee and acceptable results for testing in humans can make an investigational herbal drug qualified for a clinical trial. The complexity of herbal formulations, the synergistic effect or interactions between various constituents and regulatory issues impose a large number of challenges for the herbal medicines to be selected for clinical trials and be successfully accepted as drugs.[91] In the year 2005, WHO published a report that provides operational guidelines for clinical trials of herbal medicines. The report emphasizes that herbal drugs are faced by four major challenges that include ethical concerns, quality control procedures during manufacturing, and non-clinical and clinical issues.[92] In the recent decades, a number of herbal medicines as single herb extract or as polyherbal formulations have been subjected to testing in clinical trials. A number of reports and reviews are available that show the viability of randomized clinical trials of herbal medicines. Literature reveals many herbal formulations that were subjected to clinical trials for the treatment of neurological disorders. Many clinical trials of herbal medicines were not successfully completed due to a lack of robust study design, difficulty in the selection of specific controls, and patient-related factors.[91] Trials of medicinal plants such as St. St John's wort have failed because of low assay sensitivity and the absence of a trend in the efficacy evaluations.[69]

Conclusion

There are hundreds of natural products including individual herb and polyherbal formulations which have been characterized and evaluated for their effectiveness in various neurological disorders in preclinical experiments and randomized clinical trials. The majority of the clinical trials were non-conclusive and unable to provide strong evidence to establish the effectiveness of each natural product.[93–97] There is a huge gap in bringing these active herbs to patients in the clinics. There is an abundance of potential natural products that have not been examined yet. The strong collaborative effort between ethno pharmacologists and clinical neurologists and extensive supporting initiatives from the regulatory and governmental bodies for herbal drug research is required to overcome the challenges that herbal drugs face in their acceptance for clinical treatment.

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Conflict of interest

Authors declare that there is no conflict of interest(s)

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