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Natural Medicines Enhancing Neurite Growth in Central Nervous System Disorders: A Review

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MS, RSS and VA designed the study and performed the statistical analysis. Authors BKV, SG and BRA wrote the protocol and authors CG and DP wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aim: This review provides attention to different species of plants protecting neurons and enhancing neurite growth.
Methodology: Datas regarding the global burden of neurological disorders along with the use of different parts of the plant which provides traditional healing effect existing in some parts of the World were collected from studies carried out by several researchers.
Summary of Review: The phytochemical exploration of indigenous flora provided hundreds of CNS active plants covering the whole spectrum of activity such as psychoanaleptic, psycholeptic and psychodysleptic effects. Many studies have shown data for enhancing neurite

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outgrowth beyond neuroprotection.
Conclusion: Plants with various phytoconstituents such as flavonoids provide a safe therapeutic solution in reducing the burden of neurological disorders.

Keywords: Herbs; neurodegeneration; CNS; traditional medicines; flavanoids; neutraceuticals.

ABBREVIATIONS

A - Absorption; D - Distribution; M - Metabolism; E - Elimination; GBE - Ginkgo biloba extract; Ke - elimination rate constant; Ka - Absorption rate constant; BA-CMC - baicalin carboxymethyl cellulose solution; BA-LP - baicalin -loaded liposome; C_{max} - peak concentration; T_{max} - time of peak concentration; AUC - Area under the concentration-time curve; Cl - clearance; MRT - mean residence time; CL/F - apparent clearance.

1. INTRODUCTION

Neurological disorders are a significant and increasing public health problem. The Global Burden of Disease (GBD) study, a collaborative endeavor of the World Health Organization (WHO), the World Bank and the Harvard School of Public Health, drew the attention of the international health community to the burden of neurological disorders and many other chronic conditions. The study found that the burden of neurological disorders was seriously underestimated by traditional epidemiological and health statistical methods that take into account only mortality rates but not disability rates. The GBD study showed that over the years the global health impact of neurological disorders had been underestimated [1].

Among the non-communicable diseases [NCDs], neurological disorders form a significant proportion of global burden of disease [2,3]. Two important documents published by WHO and World Federation of Neurology bring to forefront the public health challenges posed in dealing with neurological disorders particularly in the developing countries with limited resources [4,5]. In this scenario, it is crucial to determine through neuroepidemiological approach the magnitude and pattern of neurological disorders in India to facilitate planning and prioritizing health needs at the local, regional and national levels of health care delivery system with necessary human resources, development of infrastructure, to provide accessible and affordable medical care with allocation of requisite funds to fulfill these objectives.

The growth and development of the discipline of neuroepidemiology in India, methodological issues encountered and the strategies developed to address them, analysis of data on prevalence and pattern of neurological disorders and epidemiology of selected disorders including epilepsy, stroke, Parkinson's disease and tremors.

Growth and development of neuroepidemiology in India during the last four decades has been documented highlighting the historical milestones. The prevalence rates of the spectrum of neurological disorders from different regions of the country ranged from 967-4,070 with a mean of 2394 per 100000 population, providing a rough estimate of over 30 million people with neurological disorders (excluding neuroinfections and traumatic injuries)[6].

2. EXPLORATION OF NATURAL DRUGS

Natural products remain a prolific source for the discovery of new drugs and drug leads even from Vedic period. Recent data suggests that 80% drug molecules are natural products (NPs) or natural compound inspired [7]. The phytochemical exploration of indigenous flora has contributed to some extent in this race for the discovery of new drugs. Studies on sources of new drugs from 1981 to 2007 reveal that almost half of the drugs approved since 1994 are based on natural products [8].

Many NPs have been shown to occupy different and sometimes difficult to access chemical space compared to synthetic compounds [9,10]. The uniqueness of many NP skeletons (or templates) makes these compounds of interest for use as starting points for semi-synthesis and total synthesis [11-14].

Significant number of studies has been performed to find alternatives or treatments for diseases of the nervous forum by identifying structures with activity at the central nervous

system (CNS).This medical need has led to the reemerging of modern natural products chemistry that has yielded sophisticated and complex new lead molecules for drug discovery and development. It is concluded that natural product chemistry brings tremendous diversity and historical precedent to a huge area of unmet medical need [15].

In traditional practices of medicine, plants have been used to enhance cognitive function. Plant constituents may not only act synergistically with other constituents from the same plant but may also enhance the activity of compounds, or counteract toxic effects of compounds, from other plant species. This approach has been used in various practices of traditional medicine, including Ayurveda and Traditional Chinese medicine (TCM) where a combination of plants is frequently prescribed. Plants have been used by human since immemorial times to cure diseases and to promote relief from ailments as they were most important sources of medicines for people, even though this old form of therapeutics began to lose its importance.

But nowadays such ancient use of plants was a lead for scientists in their search for new substances endowed with therapeutic property. It is estimated that nearly 25% of the modern drugs directly or indirectly originated from plants [16]. Several are the examples concerning the CNS: Caffeine, ephedrine, cannabinoids, opioids and reserpine, etc., However, for the majority of CNS active plants, the active principles are not yet known. Nature provided hundreds of CNS active plants covering the whole spectrum of activity such as psychoanaleptic, psycholeptic and psychodysleptic effects. For most of these plants, the studies are in the initial pharmacological steps, consisting of the administration of crude extracts to laboratory animals. Those initial preclinical tests frequently confirm the folk use of the plant. However, these results are, in general, far from being sufficient to prove efficacy and safety in human beings [17].

An ethnopharmacological approach may be useful in providing leads to identify plants and potential new drugs that are relevant for the treatment of cognitive disorders [18]. The pharmacological basis of some plants and their active constituents that have been used in traditional Ayurvedic medicine and TCM for their reputed cognitive-enhancing effects, plants reputed to have 'anti-ageing' or 'memory-enhancing' effects could also be considered for potential efficacy in disorders now recognized to be associated with cognitive dysfunction, including conditions that feature dementia. Plants that have shown favorable effects in relation to cognitive disorders, including anticholinesterase (anti-ChE), anti-inflammatory and antioxidant activities, or other relevant pharmacological activities indicating the potential for clinical use, are discussed.

3. PLANTS USED IN TRADITIONAL AYURVEDIC MEDICINE

3.1 *Celastrus paniculatus* Willd

C. paniculatus (Celastraceae) seeds and seed oil have been used in Ayurvedic medicine for "stimulating intellect and sharpening the memory" [19,20]. When administered orally to rats, the seed oil decreased levels of noradrenaline, dopamine and 5-hydroxytryptamine (5-HT) in the brain, which was correlated with an improvement in learning and memory processes; in addition, the oil was not shown to be neurotoxic [21].

3.2 *Centella asiatica* L

One ancient Ayurvedic remedy is *C. asiatica* (Umbelliferae), which is reputed to restore youth, memory and longevity [22]. For example, an Ayurvedic formulation composed of four herbs, including *C. asiatica*, is used to retard age and prevent dementia, and the herb combined with milk is given to improve memory [23]. An aqueous extract of *C. asiatica* leaf modulated dopamine, 5-HT and noradrenaline systems in rat brain and improved learning and memory processes *in vivo* [24]. Glutamate may induce neuronal degeneration by overstimulation of NMDA receptors. Memantine, an NMDA receptor antagonist, is licensed for the treatment of moderately severe to severe AD and it is therapeutically effective [25,26].

3.3 *Clitoria ternatea* L

The roots of the Indian medicinal plant *C. ternatea* (Leguminosae) have a reputation for promoting intellect [27,20]. Enhanced memory retention following oral administration of *C. ternatea* root extract was associated with increased levels of ACh and choline acetyltransferase (ChAT) in rat brain, but any relationship with inhibition of AChE activity was not established, and cortical AChE activity was actually found to be increased [28].

3.4 *Curcuma longa* L

Regarded as a 'rasayana' herb in Ayurveda (to counteract ageing processes), *C. longa* (Zingiberaceae), known in English as 'turmeric,' has also been used for culinary purpose. The antioxidant activity of curcumin is well documented [29-32]. Curcumin was shown to be neuroprotective against ethanol-induced brain injury *in vivo* following oral administration; an effect that was related to a reduction in lipid peroxide levels and enhancement of glutathione in rat brain [33].

4. OTHER PLANTS AS TRADITIONAL AYURVEDIC MEDICINE

In Ayurveda, herbal medicines with rasayana effects are believed be restorative, to attain longevity, intelligence and freedom from age-related disorders. *Acoruscalamus* (Araceae) root is regarded in Ayurvedic medicine as promoting rasayana effects [23] and has been used to treat memory loss. An ethanol *A. calamus* root extract and α-and β-asarone, isolated from the essential oil, are reported to exert sedative effects and potentiate hypnosis *in vivo* [34,35]. The root has also shown antioxidant activity *in vitro* [36]. More specifically, in relation to the reputed effects in traditional medicine, *A. calamus* root extract protected rats against acrylamide-induced neurotoxicity and reduced the incidence of paralysis [37]. The ripe fruit of *Terminalia chebula* (Combretaceae) is regarded as a promoter of intellect and memory, and is believed to prolong life [23,27]. The ripe fruit (unripe fruit is reported to produce different effects) is reputed to retard the ageing process and to improve cognitive processes [34], thus suggesting apparent benefits in AD. There is a general lack of research substantiating the reputed effects in Ayurveda, and only a limited number of studies provide some explanation for the reputed effects. A methanol extract is reported to bind to NMDA and GABA receptors, but did not show anti-ChE activity [38].

Numerous TCM prescriptions used for CNS disorders have also been investigated for the pharmacological basis of their activities. For example, the decoction *Banxia houpu* (composed of five herbs including *M. officinalis*) was antidepressant *in vivo* [39] and a TCM prescription, Oren-gedoku-to (Huang-Lian-Jie-Du-Tang: composed of four herbs including *C. chinensis*), has shown numerous effects suggesting it is an advantageous treatment in cognitive disorders. Antioxidant [40-42] and anti-inflammatory (including via inhibition of COX-2) activities [43-45] neuroprotection (including in the cholinergic system) against ischemia [46,47] and a protective action against impairment of learning and memory following ischemia are some of the activities that have been observed with Oren-gedoku-to.

5. NEURITE OUTGROWTH BY NATURAL PRODUCTS

Neurite outgrowth is the first step in the construction of the neuronal network, and neurite outgrowth activity has been investigated in many crude drugs. Of these extracts, several constituents have been identified as active compounds (Table 1). It is critical that extended neurites have specific functions, such as axons and dendrites, and can make circuits by synaptic connections. However, the identification of axons and dendrites and the measurement of synaptogenesis have not been undertaken in studies of natural products, apart from in our research. Ginseng drugs, Ashwagandha and coffee beans contain interesting compounds with potent neurite regeneration, synaptic reconstruction and memory improvement activities.

5.1 Pharmacokinetic Profile & Toxic Information of CNS Plants

The pharmacokinetic profile and toxic information of some of the CNS protecting natural plants are shown below:

5.1.1 *Panax ginseng* (ginsenosides)

Absolute bioavailability of Re was 7.06%; the peak plasma concentration after oral administration was 0.4±0.2 hour. Oxidation and deglycosylation were found to be the major metabolic processes of the constituent in rat, so that a large part of the intact ginsenosides was metabolized and transformed to ginsenosides. Rapidly cleared from the body within 0.2±0.03 hour for male mice and 0.5±0.08 hour for female mice after intravenous administration [48]. Adverse events have been associated with high doses and long-term usage, producing what has been cited in the literature as ginseng abuse syndrome. Side effects such as hypertension, nausea, diarrhea, headache, mastalgia, insomnia, and skin rash have been noted [49].

Table 1. Natural medicine-oriented compounds which enhance neurite outgrowth & its CNS disorder attenuation

Compounds	Main botanical source (parts used)	Cell used	Effective dose	Functions	References
Ginsenoside Rb1	*Panax ginseng, Panax notoginseng* (root)	rat cortical neuron	0.1-100 µM	axon extension, synaptogenesis, memory improvement.	[50,51]
Metabolite 1*	(protopanaxadiol-type saponins)	rat cortical neuron	0.01-1 µM	axon extension, synaptogenesis memory, improvemen.t	[51]
Withanolide A	*Withania somnifera* (root)	rat cortical neuron	1µM	axon extension, dendrite extension, synaptogenesis, memory improvement.	[52] 5[3]
Withanoside IV	*Withania somnifera* (root)	rat cortical neuron	1 µM	axon extension dendrite extension synaptogenesis memory improvement	[52]
Withanoside VI	*Withania somnifera* (root)	rat cortical neuron	1 µM	axon extension dendrite extension synaptogenesis memory improvement	[52]
Trigonelline	*Coffea arbica* (coffee bean)	rat cortical neuron	30-100 µM	axon extension dendrite extension memory improvement	[54]
Honokiol	*Magnolia obovata, Magnolia officinalis* (bark)	rat cortical neuron	0.1-10 µM	neurite outgrowth	[55]
(-)-3,5-Dicaffeoyl-muco-quinic acid	*Aster scaber* (herb)	PC12	1-10 µM	neurite outgrowth	[56]
Catalpol	*Rehmannia glutinosa* (root)	PC12h	0.1-1 µg/ml	neurite outgrowth	[57]
Geniposide	*Gardenia jasminoides* (fruit)	PC12h	0.1-10 µg/ml	neurite outgrowth	[57]
Gardenoside	*Gardenia jasminoides* (fruit)	PC12h	0.1-10 µg/ml	neurite outgrowth	[57]
Picroside I	*Picrorhiza scrophulariiflora* (root & rhizome)	PC12D	10-100 µM	potentiating NGF-induced neurite outgrowth	[58]
Picroside II	*Picrorhiza scrophulariiflora* (root & rhizome)	PC12D	0.1-100 µM	potentiating NGF-induced neurite outgrowth	[58]

Compounds	Main botanical source (parts used)	Cell used	Effective dose	Functions	References
Nardosinone	*Nardostachys chinensis* (root)	PC12D	0.1-100 μM	potentiating NGF-induced neurite outgrowth	[59]
Baicalein	*Scutellaria baicalensis* (root)	PC12	5 μg/ 50 & 200 mg	Neurite outgrowth in PC12cells	[60]
Isorhamnetin	*Ginkgo biloba* (leaves)	PC12	Isorhamnetin (10 μM) & NGF (0.5 ng/mL) coapplied	Increased expressions of neurofilament, i.e., NF68, NF160 & NF200	[61]
Curcumin	*Curcuma longa* (rhizome)	PC12	10 & 20 μM/ 0.2 mg	Neurite outgrowth in PC12 cells/ Neurogenesis	[62,63]
Rosmarinic acid	*Salvia officinalis* (herb)	PC12	10^{-8}-10^{-4} M	Increased neuroprotection	[64]

** 20-O-β-D-glucopyranosyl-20(S)-protopanaxadiol ; NGF- Nerve Growth Factor*

S.no	Plant species	CNS activity / CNS disorder attenuation activity	Reference
1.	*Panax ginseng*	Neuroprotective against Cerebral Ischemia; Modulation of proinflammatory cytokine production; Anti- Parkinsonian Effect;	[65]
2.	*Salvia officinalis*	Antioxidant Potential; Anti-inflammatory Activity; Alzheimer Disease; Dementia Amelioration;	[66]
3.	*Curcuma longa*	ischemic brain injury; Alzheimer's disease; Neuroprotective activity; Anti-inflammatory activity;	[67]
4.	*Ginkgo biloba*	Dose dependent cognitive effects; anti-ageing; Effective in dementia;	[68]
5.	*Gardenia jasminoides*	anti—apoptotic; anti-oxidant; Alzheimer's disease;	[69]
6.	*Withania somnifera*	Neuropharmacological Activity; Anti-stress/Adaptogenic Activity; Anticonvulsant Activity; Morphine Tolerance and Dependence-Inhibiting Effect;	[70]
7.	*Scutellaria baicalensis*	Iron induced neurodegeneration; anti- convulsant; prevent ischemia induced brain inury;	[71]
8.	*Mangolifera officinalis*	Central Depressant and Muscle Relaxant Effects; anxiolytic effects;	[72]
9.	*Aster scaber*	Neuritogenesis; neurite outgrowth in PC12 cells	[73]
10.	*Nardostachys chinensis*	Anti-depressant; Antioxidant Potential; Anti-parkinsonian activity; anti-cataleptic effect; anti-convulsant activity;	[74]
11.	*Picrorhiza scrophulariiflora*	Immunomodulator Action; Neuromuscular action; Anti-oxidant activity;	[75]
12.	*Rehmannia glutinosa*	Neuroprotective activity; Anti-oxidant activity; Protective effect on chronic cerebro hypoperfusion;	[76]

5.1.2 *Ginkgo biloba* (quercetin)

The initial concentration in the plasma - 171.22 µg/mL; $AUC_{0-\infty}$ - 1711.06 µg min/mL; apparent volume of distribution - 0.11 L/kg; total body clearance - 10.52 mL/(min.kg); Ka (1/h) - 0.6376; Cmax (ng/mL) - 179.21 (GBE); Ke (1/h) - 0.0541; CL/F(s) (ng/h/(ng/mL)) – 0.0015 [77]; number of acute poisonings caused by *Gingko biloba* leave extract such as increased risk of bleeding, gastrointestinal disturbances and allergic skin reactions, etc [78].

5.1.3 *Curcuma longa* (curcumin)

AUC (min µg/mL) - 7.2±1.2 (10 mg/kg, i.v.); 3.6±0.6 (500 mg/kg, p.o.); Cmax (µg/mL) – 0.36±0.05 (10 mg/kg, i.v.) & 0.06±0.01 (500 mg/kg, p.o.); Termination half life (h) – 2.3; Apparent clearance (CL/F)(L/kg) – 0.84 [77]; Curcumin blocks NF-κB and the motogenic response in Helicobacter pylori-infected epithelial cells [79].

5.1.4 *Gardenia jasminoides* (Geniposide 10 mg/kg^{-1})

AUC liver/AUC blood - 1.34±0.27; AUC bile/AUC blood - 2.50±0.33; MRT (min) - 15±1 (blood); 16±2 (liver); 37±2 (bile); Cl (ml min−1 kg−1) - 24±1 [77];

5.1.5 *Withania somnifera*

AUC_{∞} (mg/ml.h) 181.44±8.84; MRT (h) 1.34±0.045; Vdss (L/kg) 3.68±0.12; Cl (L/kg/h) 2.78±0.12 [80];

5.1.6 *Scutellaria baicalensis*

$AUC_{(0-t)}$ (mg/L*h) - 12.397 (BA-CMC); 37.64 – (BA-LP); $MRT_{(0-t)}$ (h)- 9.775 (BA-CMC); 8.358 (BA-LP); Vz (L/kg) - 142.088 (BA-CMC); 32.446 (BA-LP); CL (L/h/kg) - 3.965 (BA-CMC); 2.116 (BA-LP) [81];

5.1.7 *Magnolia obovata, Magnolia officinalis*

AUC0–480 (nmol • min/mL) - 228.5±23.2; Tmax (min) - 18.3±3.8; Cmax (nmol/ Ml - 2.6± 0.5; MRT (min) - 82.2±12.9; hydrolyzed byβ-glucuronidase or sulfatase and eliminate [72].

5.1.8 Coffea arabica

Chlorogenic acid-derived metabolites were found to be separated into two groups showing different pharmacokinetic properties. The first group comprised, e.g., ferulic acid and feruloyl sulfate and showed early appearance in the plasma (~1 h). The second group contained particularly chlorogenic acid metabolites formed by the intestinal microflora, appearing late and persisting in the plasma (>6 h). Trigonelline appeared early but persisted with calculated half-life times~5 h. The plasma levels of caffeine metabolites significantly and progressively increased 2–4 h after coffee consumption; Trigonelline (II-1), N-methylpyridinium (II-2), and the caffeine-derived dimethyl xanthines III-2 - III-4, monomethylxanthines III-5 andIII-6,as well as1,3-and/or 1,7-dimethyl uric acid were detected as key metabolites in the urine [82].

6. PHENOLIC COMPOUNDS AS NUTRACEUTICALS

The term "nutraceutical" was coined from "nutrition" and "pharmaceutical" in 1989 by Stephen DeFelice, founder and chairman of the Foundation for Innovation in Medicine (FIM), Cranford, NJ, USA [83]. When functional food aids in the prevention and/or treatment of disease(s) and/or disorder(s) other than anemia, it is called a nutraceutical [84]. Thus, nutraceuticals differ from dietary supplements in the following aspects: (a) nutraceuticals must not only supplement the diet but should also aid in the prevention and/or treatment of disease and / or disorder; and (b) nutraceuticals are used as conventional foods or as sole items of a meal or diet [86]. Polyunsaturated fatty acids (PUFAs) (which include the omega-3 and omega-6 fatty acids) and phytochemicals also play an important role as healthy dietary bioactive compounds [86]. A balanced PUFA composition of food influences diverse aspects of immunity and metabolism [86]. Phytochemicals (bioactive non-nutrient plant compounds), have raised interest in human nutrition because of their potential effects as antioxidants, anti-estrogenics, anti-inflammatory, immunomodulatory, and anti-carcinogenics [86,87].

The major active nutraceutical ingredients in plants are flavonoids. As is typical for phenolic compounds, they can act as potent antioxidants and metal chelators. They also have long been recognized to possess anti-inflammatory, anti-allergic, hepatoprotective, antithrombotic, antiviral, and anti-carcinogenic activities, as discussed in Table 2 that follow:

Table 2. Therapeutic and bioactivity of active nutraceutical ingredients

Therapeutic activity	Active constituents	Bioactivity	Reference
Antioxidant activity	Myrcetin>quercetin>rhamnetin>morin>diosmetin>naringenin>apigenin>catechin>5,7-dihydroxy-3',4',5'-trimethoxy-flavone>robinin> kaempferol>flavone17.	The flavones and catechins seem to be the most powerful flavonoids for protecting the body against reactive oxygen species (ROS). Body cells and tissues are continuously threatened by the damage caused by free radicals and ROS which are produced during normal oxygen metabolism or are induced by exogeneous damage	[88,89]
Anti-inflammatory activity	Flavone/flavonol glycosides as well as flavonoid aglycons have been reported to flavones/flavonolskaempferol, quercetin, myricetin, fisetin.	Flavonoids can modulate arachidonic acid metabolism via the inhibition of cyclo-oxygenase (COX) and lipooxygenase activity (LOX). Also, it has been speculated that the anti-inflammatory and anti-allergic properties of flavonoids are the consequence of their inhibitory actions on arachidonic acid metabolism.	[90-92]
Antineoplastic activity	Quercetin.	Exerted a dose-dependent inhibition of growth and colony formation.	[93-95]
	Kaempferol, catechin, toxifolin and fisetin.	Suppressed cell growth.	
	Genistein, an isoflavone	On screening the anti-leukaemic efficacy of 28 naturally occurring and synthetic flavonoids on human promyelocytic leukaemic HL-60 cells, it was found to have strong effect.	[96, 97] [98, 99]
Effect on central nervous system	6-bromoflavone and 6-bromo-3'-nitroflavones	Shown to displace [3H] flumazenil binding to membranes from rat cerebellum but not from spinal cord, indicating selectivity for the BZ-omega receptor subtype. They possess anxiolytic- like properties similar or superior to that of diazepam.	[100]

7. CURRENT TRENDS ON NEURO-DEGENERATION

New therapeutic strategies encompassed of drugs, which are designed specifically to act on multiple neural and biochemical targets for the treating cognition impairment, depression, motor dysfunction and neurodegeneration. Examples include the development of single molecular substance that combine two or more of the following properties: (i) cholinesterase (ChE) inhibition; (ii) activation or inhibition of specific subtypes of acetylcholine receptors or α-adrenoceptors; (iii) anti-inflammatory activity; (iv) monoamine oxidase (MAO) inhibition; (v) catechol-O-methyl transferase (COMT) inhibition; (vi) nitric oxide (NO) production; (vii) neuroprotection; (viii) anti-apoptotic activity; and (ix) activation of mitochondrial-dependent cell-survival genes and proteins. These bi-or multi-functional compounds might provide greater symptomatic efficacy and better utility as potential neuroprotective disease-modifying drugs.

8. CONCLUSION

Nature provided variety of plants having CNS activity, which covers the whole spectrum of activity such as nerve damage prevention,

neuroprotection and neurite growth, etc., [Brahmi (288 mg), Mandukaparani (140 mg), Ashvagandha (104 mg), Vishnukrantha (104 mg) – some of the marketed formulation to cure mental disorders] [101]. Those natural compounds have several great advantages over current therapeutic drugs for the following reasons:

i) Many diets are rich in these phenolics and are daily consumed.
ii) They rarely have any side effects.
iii) They have relatively long half-life.
iv) They can be easily absorbed in the intestine after ingestion.

These compounds, sourced from natural products and used with treatments not only preventing pathogenesis and neuronal death, but are also expected to play an important role as new categorized drugs in curing neurodegenerative diseases not only by protecting neuronal damage but also by enhancing neurite growth in the near future. Further, drugs used in traditional medicine may offer a treasury of new medicines to treat intractable diseases with the use of novel study concepts and the application of objective scientific analyses. It becomes a critical component which may brings change in the society with neurodegeneration.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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