

REVIEW ARTICLE

Neuroprotective Strategies for Neurological Disorders by Natural Products: An update

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Abstract: Nature has bestowed mankind with surplus resources (natural products) on land and water. Natural products have a significant role in the prevention of disease and boosting of health in humans and animals. These natural products have been experimentally documented to possess various biological properties such as antioxidant, anti-inflammatory and anti-apoptotic activities. *In vitro* and *in vivo* studies have further established the usefulness of natural products in various pre-clinical models of neurodegenerative disorders. Natural products include phytoconstituents, like polyphenolic antioxidants, found in herbs, fruits, nuts, vegetables and also in marine and freshwater flora. These phytoconstituents may potentially suppress neurodegeneration and improve memory as well as cognitive functions of the brain. Also, they are known to play a pivotal role in the prevention and cure of different neurodegenerative diseases, such as Alzheimer's disease, epilepsy, Parkinson's disease and other neuronal disorders. The large-scale neuro-pharmacological activities of natural products have been documented due to the result of either the inhibition of inflammatory processes, or the up-regulation of various cell survival proteins or a combination of both. Due to the scarcity of human studies on neuroprotective effects of natural products, this review focuses on the various established activities of natural products in *in vitro* and *in vivo* preclinical models, and their potential neuro-therapeutic applications using the available knowledge in the literature.

ARTICLE HISTORY

Received: March 04, 2018
Revised: August 02, 2018
Accepted: September 05, 2018

DOI:
10.2174/1570159X16666180911124605

Keywords: Neurological disorders, neuroprotection, plant products, nutraceuticals, natural compounds, chronic neurodegenerative diseases.

1. INTRODUCTION

Most commonly, products obtained from natural sources have been used by human beings as a leading source of medicinal agents so as to bring relief from many diseases, illnesses and frail. At the same time, people using these medicines are unaware of the side effects and poisonous nature of some natural products. The therapeutic use of plants containing these medicinal products can be traced back to the

Sumerian and Akkadians civilization [1]. Natural products have played an important role in ancient traditional medicine systems, such as Unani, Chinese and Ayurveda which are still in common use today. Plants are the best source for the isolation of secondary metabolites demonstrating significant structural diversity and offer a wide range of new and exciting pharmacophores. There are about less than 1% of approximately 250,000 higher plants that have been explored in-depth for their phytochemistry or pharmacological potential [2]. According to the World Health Organization (WHO), 75% of the world population still depends on plant-based traditional medicines for primary health care, which chiefly involve the use of plant extracts or their bioactive

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secondary metabolites. For the betterment of human health, a limitless source of molecules is present in nature in the form of herbs, spices and foods. Phytochemicals from plants are known to exert additive, synergistic or antagonistic effects on the body.

Neuroprotection refers to the mechanisms and strategies employed to defend the central nervous system (CNS) against injury due to both acute (e.g. trauma or stroke) and chronic neurodegenerative disorders (e.g. Dementia, Parkinson's, Alzheimer's, Epilepsy etc.) [3]. Herbal medicine and nutraceuticals represent an important and valuable source in prevention rather than treatment of neurological disorders [4]. In various experimental models of neurological diseases, phytoconstituents have reportedly shown to have modulatory effects on the nervous system [5]. The pathogenesis of nervous system disorders is not completely understood yet but most of the studies on different nervous disorder models mimicking key features of disease have highlighted important factors such as oxidative stress, mitochondrial dysfunction, neuro-inflammation etc [6, 7]. The models for neurotoxicity have been found to be an important tool for developing novel therapeutic strategies and assessing the efficacy and adverse effects of symptomatic treatments [8].

In addition to the above mentioned properties; neuroprotective natural products have been reported to modulate multiple signalling pathways *via* direct effects on enzymes, such as kinases, regulatory receptors and proteins [9, 10]. Many published reports suggest that natural products exert a number of their biological effects *via* remodelling of chromatin and epigenetic modifications [11]. This wide band of pharmacological or biological activities has made them suitable candidates for the treatment of neurological disorders and neurodegenerative diseases [12, 13].

Natural products and nutraceuticals work *via* a different mechanism to impart their neuroprotective effect. Many classes of chemical constituents are known to interact with the GABA_A receptor [14] e.g. diterpenes and cyclodepsipeptides selectively inhibit its activity [15]. Alkaloids, on the other hand, positively modulate the binding of muscimol to GABA receptor complex [16, 17]. Similarly, some flavonoids have proven tendency for binding to benzodiazepine site on the GABA_A receptor [18, 19 and also act as a scavenger to pro-inflammatory and neurotoxic species [20]. Several plants like *Arisaema amurense*, *Biota orientalis*, *Mentha arvensis*, *Salvia miltiorrhiza*, *Albizia julibrissin*, *Astragalus membranaceus*, *Glycyrrhiza uralensis* have been found to have an inhibitory effect on mono-amine oxidase-B (MAO-B) enzyme activity [21].

Oxidative stress, necrosis, cytotoxicity, ions imbalance, mitochondria dysfunction, cellular inflammation, apoptosis, increased blood-brain permeability, and morphological changes are pathological alterations in response to injuries, which aggravate medical conditions and give hints to screen alternative neuroprotection approaches [22].

Extensive research on identification and discovery of novel neuroprotective drugs has shown that plant extracts and their bioactive compounds together with nutraceuticals can have tremendous potential as neuroprotective candidates

against several types of neurodegenerative disorders. In this review, we briefly discuss some neurodegenerative diseases, with a focus on their prevention by natural products and nutraceuticals. We present an ethnobiological strategy, stressing on natural products for their role in neuroprotection (Fig. 1).

2. METHODOLOGY

Database searches using Google scholar, PubMed, and science direct were conducted until May 2018 to include up to date documented information in the present review. The search was limited to English language papers. For data mining, the following MeSH words were used in the databases mentioned above: neuroprotection, prevention, natural product, phytoconstituents, natural products Alzheimer's, natural products brain, natural products Parkinson's, natural products Amyotrophic lateral sclerosis, natural products Huntington's disease, natural products epilepsy, natural product ischemic brain injury, natural product peripheral nerve injury, natural products motor behaviour disorders, *in vivo* and *in vitro* studies for prevention of nervous disorders. In almost all cases, the original articles were obtained and the relevant data was extracted.

3. NEUROPROTECTIVE ROLE OF VARIOUS NATURAL PRODUCTS IN DIFFERENT NEUROLOGICAL DISORDERS

3.1. Cognitive and Motor Behavioural Disorder

Aging or pathologic state can progress to worsening of cognitive and motor functions. They share pathways of impairment which eventually cause a decline in neuronal survival [23]. The cognitive loss may emerge alone as a developmental deficit or with a set of neuropsychiatric complaints and hence claiming utilization of nootropics so as to boost cognitive potential. For the reason of their marginal side effects, medicinal plants are enormously investigated throughout the world [24]. One of the key factors promoting cognitive decline is the disruption of cholinergic neurotransmission in the brain [25]. With the growth in elderly population and inflation in life expectancy, cognitive and memory impairments linked to age-related neurodegenerative disorders that have become a considerable public health issue [26]. Neurotoxic factors which are responsible for progressive cognitive dysfunction and dementia are inflammatory cytokines, mitochondrial dysfunction, oxidative stress and excitotoxicity [27, 28].

Enrichment of cognition takes place by immunostimulation and amplification of acetylcholine synthesis [29]. In normal and cognitive deficit animals, *Tinospora cordifolia* has been found to supplement the cognition when evaluated for behavioural test [30]. Likewise, another plant *Bacopa monnieri* (BM) is a renowned nootropic and supplementation of alcoholic extract of BM has been found to improve both cognitive function and retention capacity with a decrease in retrograde amnesia in rats. Moreover, it has been shown to protect from phenytoin-induced cognitive deficit as well [31, 32]. Thus, it is utilized in the treatment of memory and attention disorders [33]. *Canscora decussata*, commonly known as Shankpushpi, has been found to inhibit acetylcholinesterase (AChE) enzyme which is involved in the hydrolysis

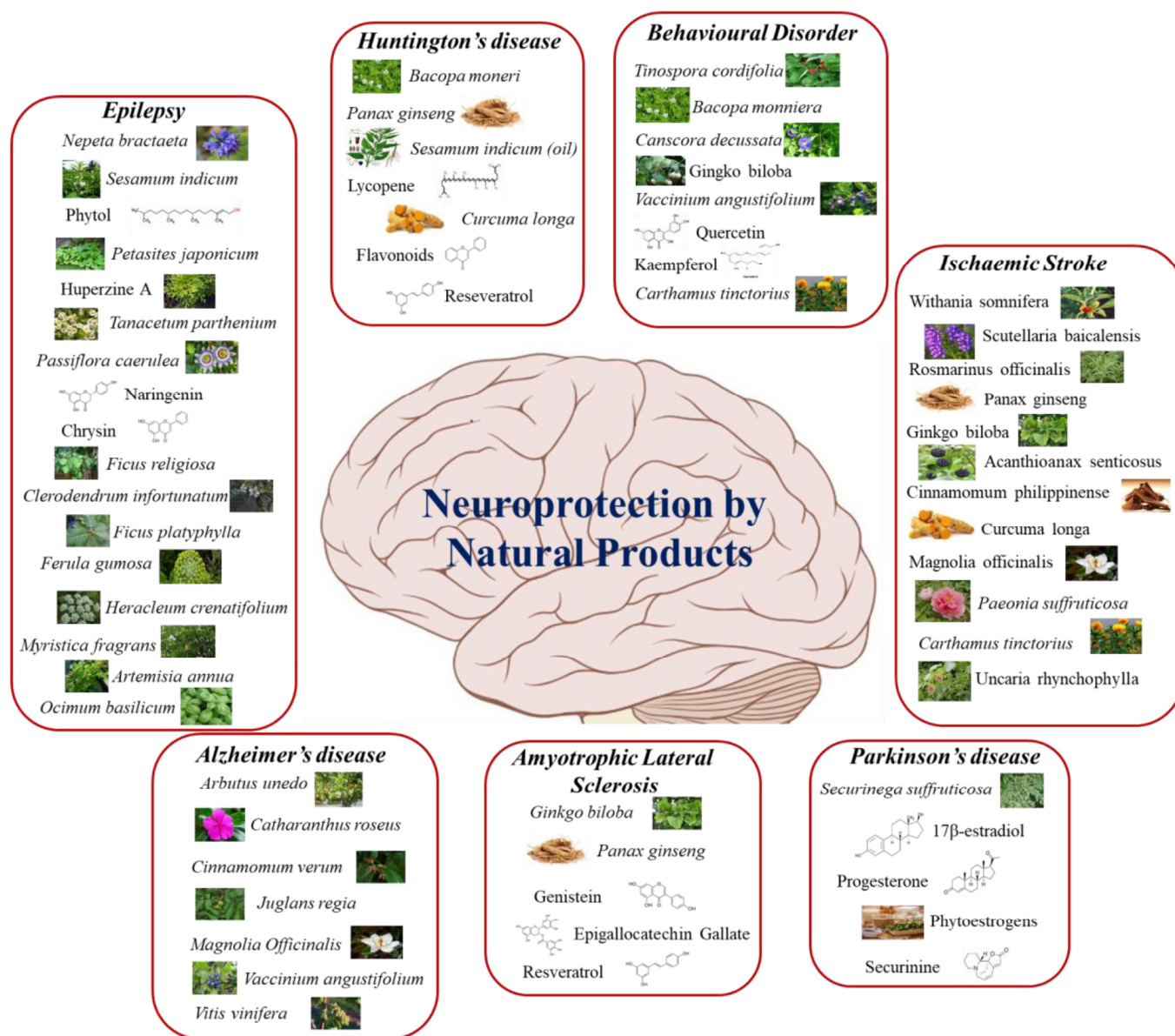


Fig. (1). Neuroprotection by various natural products. (The color version of the figure is available in the electronic copy of the article).

of acetylcholine (neurotransmitter), into choline and acetic acid, thus, AChE inhibition leads to protect the loss of acetylcholine (neurotransmitter). Acetylcholine is directly responsible for cognitive function [34]. The cognitive and memory enhancing activity of *Canscora decussata* can be attributed to mangiferin. Besides mangiferin, a significant proportion of xanthenes has been found which is responsible for the synergistic activity [35]. Cerebral ischemia and neuronal damage resulting from Alzheimer's disease (AD) and multi-infarct dementia (MID) may lead to the progression of symptoms of cognitive deficits [36]. Extensive studies have been carried out on ginkgo extract for its effects on cognition and memory in patients with dementia related to AD or cerebral insufficiency [37].

One of the richest sources of cytoprotective polyphenolic antioxidant is *Vaccinium angustifolium* (blueberry) belong-

ing to the class of anthocyanins. Preclinical studies reported that blueberry supplementation is associated with enhanced memory and motor performance in aged animals [38-42]. Since blueberry polyphenols protect muscle tissues from oxidative damage *in-vitro* they, therefore, could contribute to the amelioration of motor performance. Low levels of released lactate dehydrogenase (LDH) and creatine kinase (CK) have also been reported [43]. Blueberry supplementation in aged rats has led to amelioration of cognitive and motor performance deficits [44, 45].

Withania somnifera is a plant of medical importance which possesses several biological properties. Withanone is one of the natural compounds present in *Withania somnifera* root extract which exerts significant exhibited improvement in cognitive decline by the inhibition of amyloid β -42 in Wistar rat model. Moreover, withanone alleviates IL-6, IL-

1 β , MCP-1, TNF- α and NO levels as well as enzymatic activities of β -secretase and γ -secretase. Treatment with withanone also increased acetylcholine and GSH level and inhibited the expression of Th1 and Th2 cytokine in peripheral blood. Overall withanone exhibited improvement in cognitive decline by ameliorating inflammation and oxidative stress [46].

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a neurotoxin that has been widely used to create animal models of Parkinson's disease [47]. MPTP was accidentally discovered by a chemistry student in 1976 [48]. However, he abruptly identified the effects of MPTP administration in non-human primates and explained the mutilations that resembled the motor disabilities of idiopathic Parkinson's disease [49]. Till date, several active plant constituents have been studied to assess the neuroprotective effects against MPTP-induced motor defects. Quercetin is an important natural compound found in many plants and has been reported to improve motor defects induced by MPTP. This therapeutic effect has been associated with protection of dopaminergic neurons. Another study conducted by Li and Pu, 2011 reported a marked improvement in motor defects upon pretreatment with kaempferol. It has been reported that kaempferol recovers memory dysfunction and oxidative stress in a multi-infarct dementia model and reduces ischemic brain injury by upregulating endothelial nitric oxide synthase activity in transient focal cerebral ischemia [50]. In another study by Lu *et al.*, post-ischemic treatment with kaempferol inhibits ischemic brain damage and neuroinflammation by inhibition of STAT3 and NF- κ B activation and could be used in the treatment for the neuroinflammation associated diseases [51]. Rutong *et al.* confirmed that kaempferol 3-O-rutinoside improves behavioural performances in a 6-hydroxydopamine persuaded rodent model of Parkinson's disease, partially *via* the suppression of α -synuclein overexpression or aggregation, as well as the suppression of reactive astroglialosis [52].

Almost similar kind of results have been observed with hydroxysafflor yellow A (HSYA) from *Carthamus tinctorius* [53, 54] baicalein & baicalin [55, 56], nobiletin [57] and acacetin [58] (Table 1).

3.2. Epilepsy

Epilepsy is a serious neurological disorder identified by repetitive seizures precipitated by superfluous discharges of cerebral neurons [59]. Different limitations have been associated with the use of conventional anti-epileptic drugs (AEDs) like, inadequate seizure control, side effects, cost, potentiation of epilepsy-induced co-morbidities, *etc.*, which limit their use as a comprehensive therapy. The focus has now shifted to use natural substances (phytoconstituents) for the treatment of epilepsy. Phytoconstituents, obtained from traditional herbs, have been reported to be promising anti-epileptic drugs which can interact with most of the possible targets involved in the pathogenesis of epilepsy and can be useful in different types of epilepsy. Due to their negligible toxicity, low cost, fewer side effects compared to conventional AEDs, they have been found to be very useful and indispensable in different types of epilepsy and thus can prove to be very potent drugs for management of seizures. A dose-dependent delay in the onset of seizure and decrease in tonic hindlimb extension has been reported in pentylenetetrazole (PTZ)-induced seizure model upon treatment with aqueous and methanolic extracts of *Nepeta bracteata* [60]. Its anticonvulsant activity may be attributed to modification of glutaminergic and GABAergic transmission or blockade of sodium channels [61]. Another constituent from chlorophyll namely phytol has been reported to decrease seizure percentage and increase the latency of onset of a seizure [62, 63]. A study conducted by Costa, *et al.*, reveals the protective effect against pilocarpine-induced epilepsy and a subsequent decline in the rate of mortality. Almost similar kinds of results were obtained with sesamin, an active constituent from *Sesamum indicum* seeds. Sesamin, a

Table 1. Functions of constituents of natural products for cognitive decline.

S. No.	Natural Products-Cognitive Decline	Common Name	Constituent	Functions	Refs.
1	<i>Bacopa monnieri</i>	Brahmi	Bacosides, Bacopasides, or Bacopasaponins	Boost in retaining capability	[31]
2	<i>Canscora decussata</i>	Shankh Pushpi	Mangiferin	Inhibition of AChE	[34, 35]
3	<i>Carthamus tinctorius</i>	Safflower	Hydroxysafflor yellow A	Overcome motor deficiencies	[53, 54]
4	<i>Tinospora cordifolia</i>	Gulbel	Whole plant/ Ethanol extract	Enhancement of cognition	[29, 215]
5	<i>Vaccinium angustifolium</i>	Lowbush Blueberry	Anthocyanins	Enriched memory and motor performance	[39, 41]
6	<i>Withania somnifera</i>	Indian ginseng	Withanone	Withanone exhibited improvement in cognitive decline by ameliorating inflammation and oxidative stress	[46]

free radical scavenger and antioxidant, is known to decrease reactive oxygen species (ROS) and malondialdehyde (MDA) in epileptic kainic acid-treated mice and rats and its treatment reduces the mortality rate from 22% to 0% as well [64]. The extract of shrub *Petasites japonicum* (BMP) native to Europe is also known to possess some anticonvulsant activity. Kainic acid-treated mice when subjected to *Petasites japonicum* BMP exhibited a decline in mortality rate by 50% and decreased convulsive seizures. A remarkable decline in the loss of neurons has also been found in CA1 and CA3 regions of the hippocampus [65]. As reported by Steven *et al.*, 2009, the Swiss Webster mice when subcutaneously injected with PTZ developed seizures which were controlled by oral administration of Huperzine A, a sesquiterpene alkaloid [66].

Fruits, plant-derived beverages, herbs, vegetables and nuts are rich sources of flavonoids. Most of the flavonoids reported to have strong antioxidant potential and thus shield the cells from oxidative injury [67]. A special attention is being paid to medicinal plants as a defence against oxidative stress and epilepsy [68]. A flavone glycoside baicalin preserves levels of endogenous enzymes, increases levels of GABA in the brain in addition to the suppression of oxidative stress [69]. In adult Sprague Dawley rats, it has shown positive results as an anticonvulsant and neuroprotective against pilocarpine-induced epilepsy [70]. A well-known flavone apigenin found to be present in *Tanacetum parthenium* has reported to decrease locomotor activity and latency of the onset of a seizure in picrotoxin mice model [71]. Studies conducted on chrysin, a constituent of *Passiflora caerulea* (passion flowers) have exhibited anticonvulsant properties *in vivo*. Previous reports have recorded the abolition of PTZ-induced tonic-clonic seizures upon intracerebroventricular injection of chrysin [72]. Naringenin, a very potent flavanone, has a wide range of biological activities and exerts tremendous positive activity on benzodiazepine site of GABA receptor by finding its way to cross the blood-brain barrier [73]. Naringenin could be a promising drug for the prevention of pilocarpine-induced epilepsy due to its potential to limit oxidative stress. It has shown to decrease seizure severity, increase latency of onset of a seizure and has shown protective effects at cerebral level [69]. In the ailments that emerge as epileptic co-morbidity and the disorders that enhance epilepsy, saponins have known to play a critical role [41, 75]. For the management of epilepsy, the traditional methods of medicine utilized the adventitious roots of *Ficus religiosa* for centuries. In PTZ-induced kindling epileptic mouse model, Damanpreet *et al.*, reported the amendment in depression associated to kindling. This discovery has been supported by the alteration of cerebral neurotransmitter levels [76]. An extract of saponin rich fraction of *Ficus religiosa* has found to have anticonvulsant effects and moreover, several saponins have been labelled to acquire seizure abolishing properties [74, 77-79]. Saponins from *Clerodendrum infortunatum* have reported to decrease the time interval of seizures and they have shown a dose-dependent effects against convulsions induced by leptazol [80]. The possible mechanism behind the analgesic and anticonvulsant activity can be the elevation in serotonin and GABA levels of the brain [81-83]. The saponin-rich fraction obtained from *Ficus platyphylla* stem bark has exhibited

protection against strychnine and pentylenetetrazole-induced seizures. A momentous delay has been observed in the onset of tonic seizures and myoclonic jerks. Impairment of membrane excitability, a property demonstrated by most anti-epileptics predominantly by the voltage-gated sodium channel (VGSC) obstructing drugs, has also been reported [84].

Because of the presence of volatile oils and other chemical components, a number of classes of aromatic herbs are being investigated for therapeutic purpose. A number of aromatic herbs have been utilized conventionally as they possess strong CNS activities in addition to anti-epileptic action. In mice, the supplementation of the essential oil from fruitlets of *Ferula gumosa* has been shown to reduce tonic seizures induced by pentylenetetrazole. As the effective dose is near to LD₅₀, therefore it has shown to cause neurotoxic effects. The anti-epileptic effects of the oil may be attributed to pinene while as the neurotoxicity might be credited to α -thujene [85]. Tosun *et al.*, [86] detailed the protective effects of octyl acetate and octano from fruits of *Heracleum crenatifolium*. The essential oil has exhibited noteworthy abolition of seizures induced by maximal electroshock (MES) in mice. The oil from kernels of *Myristica fragrans* (nutmeg oil) has reported to abolish the tonic hindlimb extension prompted by maximal electroshock (MES). A substantial postponement in strychnine induced tonic extensor jerks of the hind limb has been affirmed. Against pentylenetetrazole-induced tonic seizures, nutmeg oil has shown dose-dependent anticonvulsant activity. The exact mechanism is still unknown but Wahab *et al.* reported that nutmeg oil exerts anti-convulsant effects through induction of neurotransmission mediated by GABA and reported that it interacts with sodium channels of the neurons. Hence, the nutmeg oil has proved to be an anti-convulsant at lower doses [87]. There has been a major deferral in latency of onset in pilocarpine and picrotoxin-induced seizures by using the essential oil of *Artemisia annua* and ethanolic extract acquired from fresh leaves of *Artemisia annua*. But the onset of seizures induced by strychnine and pentylenetetrazole has reported to be prevented using essential oil as well as ethanolic extract of fresh leaves of *Artemisia annua* [88]. Both essential oil and extract do not have the ability to bind glycine receptors as agonists, but can bind as glycine receptors antagonists, thus enhance the onset of convulsion. Alternatively, the latency time for the onset of convulsion onset can be increased due to depressive activity on the central nerves system but not related with GABA mechanisms [88].

Ocimum basilicum is an essential oil (EO) and the composition of eugenol is around 9% [89]. Koutroumanidou *et al.* and Okoli *et al.* reported that EO isolated from *Ocimum basilicum* plants exerts anticonvulsant effects against pentylenetetrazol-induced seizures and seizure latency in mice model [90, 91]. The treatment with EO of *Ocimum basilicum* isolated from leaves exerts CNS depressant activity. EO of *Ocimum basilicum* also enhances the latency for the onset of convulsions in pentylenetetrazol- and picrotoxin-induced seizures in mice model. The effects of EO of *Ocimum basilicum* were reversed by flumazenil which is an agonist of GABA_A receptors thus supporting a finding that *Ocimum basilicum* EO exerts anti-convulsant effects by targeting GABAergic neurotransmission mechanism. Furthermore,

Ocimum basilicum EO has not shown anti-convulsant effects using strychnine-induced seizures in mice model as strychnine induces convulsions by antagonizing glycine receptors activity and enhancing postsynaptic excitability and ongoing activity in the spinal cord and brain stem but not related to GABA receptor. Thus, *Ocimum basilicum* EO produces anti-convulsant effects by modulating GABAergic neurotransmission [92].

A natural compound alpha-asarone (α -asarone) obtained from a Chinese herbal medicinal plant that is *Acorus gramineus* which is widely used clinically for the treatment of epilepsy. It has also been shown to possess neuroprotective property and also reported to induce glutamate uptake and decrease excitation of synapses. It is clinically already proven that α -asarone induces sedative and anticonvulsant effects on the central nervous system (CNS). A study was conducted using *in-vitro* and *in-vivo* models to understand the anti-epileptic effects of α -asarone *via* elucidating the mechanism of action and therapeutic targets of α -asarone. It was found that α -asarone is an inhibitor of the hippocampal neuronal activity and thus induces anti-epileptic effects in the CNS by increasing tonic GABAergic neuronal inhibition [93].

Another plant source natural product, Cannabidiol isolated from marijuana plant is a non-psychoactive compound. In a study conducted by Hess *et al.* [82] to assess the efficacy, safety and tolerability of Cannabidiol as an adjunct therapy along with anti-epileptic drugs on the patients suffering from tuberous sclerosis complex whose most common neurological symptom is epilepsy. In this clinical trial study, after treatment with Cannabidiol, responder rate of the patients suffering from refractory seizures was 50%. After the 3 months of the treatment with Cannabidiol, patients exhibited reduced occurrence of weekly seizure by 48.8 median percent. Furthermore, cognitive enhancement in 85.7% cases and behavioural improvement in 66.7% cases have been reported by the parents of all the patients. Besides the efficacy of Cannabidiol, most of the adverse effects associated with Cannabidiol were transient in nature and resolved by dose change of Cannabidiol [94].

Flavonoids are the natural polyphenols found to be present abundantly in plants, fruits and vegetables. They have been reported to have promising anti-seizure and anti-epileptic effects which are mainly attributed due to their allosteric modulation of GABA_A receptors and anti-inflammatory effects. But the potency of the flavonoids is generally hindered due to low oral bioavailability and low metabolic stability. It has been reported that chemical modification by methylation of the free hydroxyl (OH-) group of the flavonoids can drastically improve absorption, bioavailability, membrane transport and metabolic stability. Naringenin, kaempferol and different methylated forms naringenin and kaempferol (naringenin 7-O-methyl ether, naringenin 4',7-dimethyl ether, and kaempferide (4'-O-methyl kaempferol)) were used to assess the anti-epileptic effects using pentylenetetrazole-induced seizure model of zebrafish. It was found that only naringenin 7-O-methyl ether and naringenin 4',7-dimethyl ether are very effective against pentylenetetrazole-induced seizure in larval zebrafish while naringenin, kaempferol and kaempferide have insufficient anti-seizure

effects. Additionally, naringenin 4',7-dimethyl ether is also effective against acute seizure mice models (timed intravenous pentylenetetrazole convulsive seizure model and 6 Hertz (Hz) psychomotor seizure model). Thus methylation of naringenin leads to enhance the efficacy against seizures thus has anti-epileptic effects [95] (Table 2).

3.3. Alzheimer's Disease

Alzheimer's disease (AD) is a severe, chronic and progressive neurodegenerative disease characterized by impairment in memory and cognitive function. It is usually an age-related problem. The disease was first diagnosed and described by a German physician "Alois Alzheimer" in 1906 [96]. Alzheimer's disease is affecting the aging population worldwide and has been expected to reach 106.8 million by 2050 [97]. The main pathogenesis of the Alzheimer's disease is the formation of amyloid- β (A β) fibrils which contain β -amyloid peptides. The exact mechanism for the formation of amyloid plaques is unclear but the plausible mechanism is thought to be that A β is generally produced and aggregated within the extracellular matrix to form plaques. These A β plaques are reported to be toxic for the adjacent neurons. The A β also reported to be accumulated within the neurons which lead to synaptic dysfunction, cognitive impairment and A β plaques formation [98]. Various effective therapeutic molecules have been reported to suppress the formation of A β plaques for the treatment of Alzheimer's disease [99, 100]. Keeping in view the cost of treatment for Alzheimer's disease and the limitations associated with the previous preventive techniques, natural products including nutraceuticals have gained paramount importance [5]. The natural products have been found to restore memory and cognitive deficits in the brain. The curative effects of these products are mainly due to the action of phytonutrients on distinct signalling pathways associated with protein folding and neuroinflammation. Several studies conducted on patients with AD have revealed the oxidative stress in the affected parts of the brain [101]. Reports from Pappolla, *et al.*, [102]. Heo and Lee., [103] reveal that the constituents from *Arbutus unedo*, have a very strong antioxidant potential against hydrogen peroxide-induced neurotoxicity in PC12 cells. This antioxidant potential may be endorsed to various phytoconstituents like anthocyanins, gallic acid, tannins, vitamin C, vitamin E and carotenoids. Anthocyanins from *Vaccinium angustifolium* exhibited protection from oxidative injury. Likewise, resveratrol from *Vitis vinifera* has exhibited alleviation of inflammation and oxidative stress through activation of sirtuin-1 and hence reduced expression of NF- κ B [104]. Neuropathology of AD is characterized by the formation of neurofibrillary tangles which results from the deposition of extracellular amyloid plaques and accumulation of intracellular hyperphosphorylated neuronal microtubule-associated protein known as "tau proteins" [105]. Therefore, AD is the result of mutations in the gene that forms amyloid precursor protein (APP) thus leading to altered production of peptide and contribution in loss of neurons and synaptic connections. *Juglans regia* is known to aid in the inhibition of A β fibril formation, defibrillation of the preformed A β and amyloidogenic action. The constituents responsible for this action are fatty acids, α -tocopherol, vitamin and polyphenols, especially ellagic acid present in it [106]. Almost a similar type of activity has been

Table 2. Functions of constituents of natural products for epilepsy.

S. No.	Natural Products-Epilepsy	Common name	Constituent	Functions	Refs.
1	<i>Artemisia annua</i>	Sweet wormwood	Essential oil assimilated from fresh leaves	Escalation in latency of onset of seizures	[88]
2	<i>Chlorophyll</i>	Chlorophyll	Phytol	Increased latency of seizure onset	[62, 63]
3	<i>Clerodendrum infortunatum</i>	Hill glory bower	Saponins	Diminished time interval of seizures	[80]
4	<i>Citrus fruits</i>	-	Naringenin	Drop in seizure severity	[73]
5	<i>Ferula gumosa</i>	Galbanum	Pinene	Protection against PTZ provoked seizures	[82]
6	<i>Ficus platyphylla</i>	Broadleaf fig	Saponin rich fraction	Defense in response to strychnine & PTZ incited seizures	[84]
7	<i>Ficus religiosa</i>	Sacred fig	Saponin rich fraction	Modification of cerebral neurotransmitter levels	[76]
8	<i>Fruits, plant derived beverages, herbs</i>	-	Flavonoids	Antioxidant activity	[72,95]
9	<i>Heracleum crenatifolium</i>	Cow parsnip	octyl acetate; octano	Termination of maximal electroshock (MES) induced seizures	[86]
10	<i>Myristica fragrans</i>	Nutmeg	oil from kernels	Anticonvulsant activity against MES, Strychnine and PTZ stimulated seizure	[87]
11	<i>Nepeta bracteata</i>	Catmint	Flower extracts	Alteration of glutaminergic and GABAergic conduction	[61]
12	<i>Acorus gramineus</i>	Japanese Sweet Flag	α -asarone	Inhibit hippocampal neuronal activity	[90]
13	<i>Cannabis sativa</i>	Marijuana plant	Cannabidiol	Suppressed weekly seizure, cognitive enhancement, behavioural improvement	[91]
14	<i>Citrus fruits, and other plants</i>	-----	Naringenin 4',7-dimethyl ether	Anti-epileptic effects by suppressing seizures in zebrafish and mice model	[79, 95]

reported by Frydman, *et al.*, [107] in *Cinnamomum verum*; cinnamaldehyde, eugenol, cinnamyl acetate and cinnamyl alcohol are largely responsible for its anti-Alzheimer's disease activity through blockade of oligomer and amyloid fibril formation.

Bromelain is a proteolytic enzyme found profusely in fruit and stem of pineapple. It has been reported that bromelain interacts and degrades synthetic amyloid- β 42 monomers and oligomers. Cerebro-spinal fluid (CSF), isolated from the Alzheimer's disease patients when incubated with bromelain leads to decreased level of amyloid- β 42 monomers and low oligomers thus bromelain has a strong potential to be used as a therapeutic compound for the treatment of Alzheimer's disease [108].

A recent therapeutic progress in the field of AD is the discovery of acetylcholinesterase (AChE) inhibitor. The basis of this finding is thought to be the affected cholinergic pathways in the cerebral cortex and basal forebrain in AD [109] and therefore the consequential cholinergic insufficiency adds to the cognitive damage [110]. Caffeoylquinic acid, flavonoids, citric acids from *Catharanthus roseus* can prove to be beneficial in AD patients because of their property to inhibit AChE enzyme [111]. Likewise, AChE inhibitory and memory boosting capacity of *Magnolia officinalis* has been

attributed to the presence of magnolol, honokiol, obovatol and 4-O-methylhonokiol [112] (Table 3).

3.4. Parkinson's Disease

Parkinson's disease (PD) is the second most common chronic neurodegenerative disorder, which affects movements. Loss of dopaminergic neurons in the region of substantia nigra of the basal ganglia is a characteristic feature of PD which results in postural instability, tremors, bradykinesia, rigidity and progressive loss of muscular coordination and balance [113]. The pathological hallmark of the disease is a protein called as α -synuclein that binds to ubiquitin and forms cytoplasmic inclusions referred to as "Lewy bodies" which are round eosinophilic intraneuronal filamentous inclusions [114] thereby causing degeneration of the dopaminergic neurons [115]. The disease has been found to be associated with several biochemical abnormalities in the brain including deficiency of mitochondrial complex I, depletion of intracellular thiols and increased nigral iron content [116].

PD is difficult to cure and available treatments are only symptomatic. The gold standard treatment for PD uses dopamine precursor l-3,4-dihydroxyphenylalanine (L-DOPA) which decreases the motor symptoms. However, it is associ-

Table 3. Functions of constituents of natural products for alzheimer's disease.

S. No.	Natural Products-Alzheimer's Disease	Common Name	Constituent	Functions	Refs.
1	<i>Arbutus unedo</i>	Strawberry tree	Anthocyanins, gallic acid, tannins, vitamin C, vitamin E and carotenoids	Antioxidant potential against hydrogen peroxide induced neurotoxicity in PC12 cells, improvement of memory and augmentation of spatial learning	[105, 103]
2	<i>Catharanthus roseus</i>	Madagascar periwinkle	Caffeoylquinic acid, flavonoids, citric acids	Inhibition of AChE	[111]
3	<i>Cinnamomum verum</i>	Cinnamon	Cinnamaldehyde, Eugenol, Cinnamyl acetate, and cinnamyl alcohol	Blockade of oligomer and amyloid fibril formation	[107]
4	<i>Juglans regia</i>	Persian walnut	Fatty acids, alpha tocopherol, vitamin and polyphenols, especially ellagic acid	Inhibition of A β fibril formation, defibrillation of the preformed A β and amyloidogenic action	[104]
5	<i>Magnolia officinalis</i>	Houpo	Magnolol, honokiol, obovatol and 4-O-methylhonokiol	AChE inhibitory and memory boosting capacity	[112]
7	<i>Vaccinium angustifolium</i>	Lowbush blueberry	Anthocyanins	Lowering of oxidative injury and drop in the expression of age-linked protein, such as NF- κ B	[216]
8	<i>Vitis vinifera</i>	Grape vine	Resveratrol	Mitigation of inflammation and oxidative stress via activation of sirtuin 1 and therefore weakening of NF- κ B activity and apoptotic activity of FOXO proteins	[217]
9	<i>Ananas comosus</i>	Pine Apple	Bromelain	Degrades amyloid- β 42 monomers and oligomers in CSF of AD patients. and also degrades synthetic forms.	[108]

ated with complications including L-DOPA-induced dyskinesias and others [117]. To overcome the side effects associated with the synthetic products, scientists have nowadays shifted to the use of different natural products.

Estrogenic compounds such as 17 β -estradiol and progesterone are reported to have neuroprotective effects [118]. 17 β -estradiol and naturally occurring plant-derived compounds like phytoestrogens found to have neuroprotective effects via activation of receptors like estrogen receptor- α (ER α), ER β , or G-protein coupled receptor-1 (GPER1) and stimulation of the signaling cascades including (a) extracellular regulated kinase-1 (ERK1)/ERK2, (b) PI3K/Akt, and (c) c-Jun amino-terminal kinase (JNK), which regulate various downstream transcription factors implicated in the survival of the neurons [119, 120]. ER α , in the active form, can bind to insulin-like growth factor (IGF)-1 receptor and thus regulate the signalling pathway involved in the neuroprotective action that is PI3K/Akt-glycogen synthase kinase-3 β (GSK3 β)- β -catenin [119, 121]. The expression of the anti-apoptotic proteins such as Bcl-2, Bcl-xL and Bcl-W was enhanced while the expression of the pro-apoptotic proteins such as BCL2L4 and BAD was reduced by the activated ERK1/ERK2 and PI3K/Akt signalling pathways [62, 122, 123]. 17 β -estradiol leads to the activation of JNK pathway which results in enhanced expression of anti-apoptotic proteins such as Bcl-W and BCL2L11 (BIM) [124]. The common downstream molecule of ERK1/ERK2 and PI3K/Akt signalling pathways is GSK3 β which gets activated and induces neuronal cell death, therefore, inhibition of GSK3 β promotes the survival of neurons [125].

Different spices including turmeric, ginger, pepper, cloves have been found to possess neuroprotective effects against PD [126, 127]. Consumption of green tea is beneficial against age-related neurological conditions and delayed onset of PD [128]. Securinine, a major natural alkaloid product from the root of the plant *Securinega suffruticosa*, has been reported to be a potential candidate for the treatment of neurodegenerative diseases related to neuroinflammation including Parkinson's disease [129]. Neuroprotection is due to anti-inflammatory effects of securinine in glial cells. Securinine causes inhibition of the inflammatory mediator NF- κ B, mitogen-activated protein kinases (MAPK) and also causes inhibition of interferon- γ (IFN- γ), reduces mRNA expression for inducible nitric oxide synthase (iNOS) and decreases the level of nitric oxide (NO) level. Probiotics are live microorganisms that when administered in adequate amounts, confer health benefits to the host [130]. Potential probiotics on brain functions have been shown to be dependent on vagal activation [131]. Probiotics have been found to increase the concentration of dopamine by the production of L-DOPA, a precursor of dopamine that can cross the protective blood-brain barrier which then gets converted into dopamine with the help of DOPA decarboxylase enzyme [132] (Table 4).

3.5. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal disease and the exact cause of ALS is unknown which is characterized by gradual progressive deterioration of upper motor neurons (UMNs) and lower motor neurons (LMN) [133]. The UMN

Table 4. Functions of constituents of natural products for parkinson's disease.

S. No.	Natural Products-Parkinson's Disease	Common Name	Constituent	Functions	Refs.
1	Estrogenic compounds	-	17 β -estradiol and progesterone	Neuroprotective effects	[118]
2	Natural polyphenolic compounds	-	Phytoestrogens	Neuroprotection <i>via</i> activation of receptors	[119, 120]
3	<i>Securinega suffruticosa</i>	Yi ye qiu	Securinine	Neuroprotection due to anti-inflammatory effects	[129]
4	Sex hormones	-	17 β -estradiol	Neuroprotection <i>via</i> of receptor activation	[118, 119, 121, 122]

findings include hyperreflexia, extensor planar response and spasticity. This results from the degeneration of the lateral corticospinal tract in the spinal cord. While the LMN findings include hyporeflexia, weakness, atrophy, and fasciculation. ALS is eventually fatal because of respiratory muscle weakness. Until recently, riluzole is the only Food and Drug Administration (FDA) approved medication available and also recommended by the Institute for Clinical Excellence. It can marginally ameliorate respiratory failure and enhance the survival time up to 3 months only. On the other hand, it shows no beneficial effect on muscle wasting, atrophy, spasticity, weakness, dysarthria, dysphagia and life quality of ALS patients [134].

Ginkgo Biloba contains beneficial terpenes trilactones known as ginkgolides and sesquiterpene trilactones bilobalide. Ferrante *et al.*, [133] examined the gender-specific neuroprotective effect of oral administration of *Ginkgo biloba* extract against mitochondrial damage and oxidative stress in transgenic mice model of ALS. The extract of the *Ginkgo biloba* exhibited significant improvement in motor performance and survival and ameliorated the loss of anterior motor neurons in male mice. It also showed a significant improvement in weight loss in both the genders thereby providing the strong evidences of its neuroprotective effects [133]. Similarly Ginseng has around 20 ginsenosides like protopanaxatriol and protopanaxadiol which are pharmacologically active constituents of ginseng. Jiang *et al.*, 2000 described the beneficial effects of ginseng in transgenic mice in motor impairment and survival associated with ALS. It showed the prolongation in the onset of signs and survival and provided evidence for the ameliorative effects of ginseng in ALS [135].

Another study by Trieu *et al.*, studied the effects of genistein treatment for its protection against pathological conditions like ALS and stroke. Genistein exhibits protection against singlet-oxygen induced cerebral damage *in vivo* by delaying the onset and reducing the mortality rate in G93A mice [136]. Epigallocatechin gallate (EGCG) from green tea is a bioactive natural constituent having a number of pharmacological actions like anticancer, anti-inflammatory, antioxidants *etc.* Koh *et al.*, studied the role of EGCG in oxidative stress-injured motor neurons *via* PI3K/Akt and GSK-3 pathways. Pretreatment of the cells with EGCG before oxidative exposure increased the cell viability by enhancing the survival signals. They proved that EGCG induces the activa-

tion of PI3K/Akt and inhibits GSK-3 and may be a potential therapeutic strategy for ALS [137]. Another pharmacologically active compound, resveratrol, found in red wine, peanuts, grapes and berries *etc.* has antioxidant, anti-aging, anti-Alzheimer's disease, anti-inflammatory and neuroprotective properties. Yanez *et al.*, described the protective effects of resveratrol against neurotoxic effects produced by cerebrospinal fluid in cortical motor neurons primary culture. Resveratrol mitigated the Ca²⁺ elevation produced by ALS and acts as a neuroprotective compound with potential therapeutic application in ALS patients [138] (Table 5).

3.6. Huntington's Disease

Huntington's chorea or Huntington's disease (HD) was initially defined by an Ohio physician named George Huntington. Falling into the class of inherent autosomal dominant neurodegenerative disorder, it is differentiated by augmented motor impairment along with chorea and dystonia, emotional imbalance, memory, weight loss, personality changes and diminished capability to think clearly [139-142]. With juveniles being chiefly afflicted, it can transpire between 30 and 50-year populations [143]. The pathological backbone of neurodegenerative illness is oxidative stress (OS). Degeneration of antioxidant processes and elevated markers of reactive oxygen species (ROS) production initiate death of neuronal cells [144, 145]. Mother nature is an unbeaten and unparalleled expert having cure to probably maximum ailments of a man. Of all the medicinally relevant/active plants, several have complete pharmacological influence over the body. In neurodegenerative diseases, the beneficial therapeutic effects of these plants are manifested as antioxidant, anti-inflammatory, anti-apoptotic, calcium antagonization and modulation of neurological function [146, 147]. Numerous drugs dominant to CNS have been recognized as bright anti-Huntington's disease competitors some of which include *Bacopa monnieri*, *Cannabis sativa*, *Centella asiatica*, *Gastrodia elata*, *Ginkgo biloba*, *Panax ginseng*, *Withania somnifera* *etc.* Neuroprotective compounds such as curcumin, EGCG, ginsenosides, kaempferol, naringin, resveratrol and S-allylcysteine have been certified of their anti-Huntington's disease property [148]. *Bacopa monnieri* (BM) can prove efficacious in HD therapy as its potential for being a powerful antioxidant and preventive action in opposition to stress-mediated neuronal impairment. Studies conducted on dietary BM additives have shown to produce a significant impact on brain against oxidative damage instigated by neurotoxicants

Table 5. Functions of constituents of natural products for amyotrophic lateral sclerosis.

S. No.	Natural Products-Amyotrophic Lateral Sclerosis	Common Name	Constituent	Functions	Refs.
1	<i>Ginkgo biloba</i>	Ginkgo	Terpenestriactones (ginkgolides A,B,C and J) Sesquiterpene trilactones (bilobalides), flavonol glycosides (myricetinkaempherol and quercetin)	Cognitive / memory enhancement	[197, 199, 218]
2	<i>Panax ginseng and other species</i>	Ginseng	Ginsenosides (protopanaxadiol and protopanaxatriol)	Antioxidant, anti-inflammatory	[135, 219]
3	<i>Genistein</i>	Genistein	4,5,7-trihydroxyisoflavone	Anti-viral, anti-angiogenic	[136, 220]
4	<i>Epigallocatechin Gallate (EGCG)</i>	Catechin	Flavan-3-ol	Antioxidant, anti-inflammatory	[137, 221]
5	<i>Resveratrol</i>	Resveratrol	3,5,4-trihydroxy trans stilbene	Anti-aging, anti-ischemic	[138, 223]

[149]. The other compounds from plant sources which can be used in HD as antioxidants are sesamol (from sesame oil), celastrol and lycopene. Celastrol is a triterpenoid quinone methide while lycopene is a renowned carotenoid found in substantial amounts in tomatoes and tomato-based products [150, 151]. Sesamol has shown to produce protective effects against 3-nitropropionic acid (3-NP)-induced HD [152]. An additional nitric oxide pathway in neuroprotection has been reported to be traced by lycopene [153, 154]. Flavonoids are also known to inhibit nitric oxide synthase and therefore delaying progression of HD [152-157].

Operating as an irreversible inhibitor of succinic acid dehydrogenase (SDH), in rats, the neuronal disruptions incited by 3-Nitropropionic acid are very similar to disorders in patients with Huntington's disease [158]. Curcumin, a substance in turmeric has reportedly improved body weight, abolished motor defects and inflated SDH activity in 3-NP treated rats [159]. Resveratrol, a naturally occurring phytoalexin, can hamper or modify the development of neurological ailments like HD and ischemic stroke. The 3-NP instigated cognitive and motor defect can also be reversed by resveratrol [155, 160]. Upon treatment with resveratrol, improvement of locomotor activity and maze performance has been reported in animal model of HD [160].

In addition to excitotoxicity, an increase in malondialdehyde (MDA), heme-oxygenase, 3-nitrotyrosine has been detected in the brains of HD patients and rodents [161-163]. Ginseng root is a well-known herbal drug. Besides possessing antioxidant properties, it maintains the constitutional stability of neurons, improves cognitive capacity, restricts excitotoxicity and excess inflow of Ca^{2+} in neurons. There has been also a reduction in lipid peroxidation [164, 165]. A reducing sugar trehalose can be employed in emerging a novel therapeutic drug for HD as it possesses both the properties of inducing autophagy and chemical chaperone [166] (Table 6).

3.7. Peripheral Nerve Injury

The peripheral nervous system (PNS) is a highly complex system composed of the cranial and the spinal nerves

which project from the spinal cord and then pass through the intervertebral foramina of the vertebrae [167]. Peripheral nerves are present in nearly all parts of the human body and are composed of both motor and sensory neurons [168]. Fractures, lacerations, crush injuries, scars, compression or some iatrogenic ways result in the injury of these peripheral nerves [169]. If such nerve injuries are left untreated, there may be a partial or total loss of sensory, motor and autonomic functions resulting in restricted activity or lifelong disability [170]. Desirable motor and sensory recovery after peripheral nerve injury is a clinical challenge and uses different neurotrophic drugs like methylprednisolone and gabapentin, steroids, hormones, and even low-dose radiation has been reported [171, 172]. However, their adverse effects are a major limitation associated with their clinical use.

High chemical diversity, biochemical specificity and several other molecular properties of the drugs obtained from natural products make them favourable for the treatment of nerve injuries and associated symptoms such as neuropathic pain [173, 174]. Primarily, peripheral nerve injury is followed by secondary ischemic injury and is dominated by inflammation. Vitamin B12, also called cobalamin, is naturally present in fishes and animal products like meat, eggs, milk and milk products [175]. It is a water-soluble vitamin with multiple functions in organisms, although it is required in minute quantities. Vitamin B12 acts as a coenzyme and facilitates the synthesis of nucleic acids and proteins *via* conversion of homocysteine to methionine. It accelerates the formation of the myelin sheath, promotes the neuraxon's skeleton protein transportation and improves nerve conduction velocity [176]. Moreover, vitamin B12 has been reported to cause proliferation of Schwann cells and increases the diameter of axons [177]. Also, vitamin B12 is a good scavenger of reactive oxygen species and is well-known for antioxidant properties and neuroprotective role. In addition, vitamin B12 promotes regeneration and functional recovery of injured nerves through increased expression of brain-derived neurotrophic factor (BDNF) at both mRNA and protein levels [178]. Thiocetic acid, also known as α -lipoic acid, is another biological antioxidant and detoxifying agent. It is proposed to be good for treating diabetic neuropathy, cogni-

Table 6. Functions of constituents of natural products for huntington's disease.

S. No.	Natural Products-Huntington's Disease	Common Name	Constituent	Functions	Refs.
1	<i>Bacopa monnieri</i>	Brahmi	Leaf powder	Protective effect on brain against oxidative damage	[149]
2	<i>Panax ginseng</i>	Five fingers	Root	Maintenance of neuronal constitutional stability, improvement of cognitive capacity	[164, 165]
3	<i>Sesamum indicum (oil)</i>	Sesame	Sesamol	Protective effects against 3-NP induced HD	[64]
4	<i>Tomatoes and tomato-based products</i>	-	Lycopene	Antioxidant activity, additional nitric acid pathway in neuroprotection	[153, 154]
5	<i>Curcuma longa</i>	Turmeric	Curcumin	Obliteration of motor defects and inflation of SDH activity	[126, 163, 203]
6	<i>Several fruits and vegetables</i>	-	Flavonoids	Inhibition of nitric oxide synthase	[156, 157]
7	<i>Several plants particularly grapevines</i>	-	Resveratrol	Improvement of locomotor activity and maze performance	[138, 160, 222, 223]

tive and neuromuscular deficits, countering age-associated cardiovascular and as a modulator of various inflammatory signalling pathways [179, 180]. Thioctic acid's role as an agent interfering in liver metabolism and disease was also reviewed [181]. Due to the presence of an asymmetric carbon C3, thioctic acid exists in two enantiomers, namely, (+) and (-). The (-) enantiomer probably represents the active form of the compound which elicits the biological effects and is located intracellularly. Thioctic acid is a registered drug used worldwide as a nutraceutical and it is marketed mainly in the racemic (+/-) form for stability reasons. Thioctic acid has also been found to be effective against the central nervous system lesions which are consequent to peripheral nerve injury [181, 182].

Acetyl-L-carnitine (ALCAR) is a physiological peptide which also has some inherent antioxidant properties and ability to enhance the nerve growth factor binding capacity to receptors present on sensory neuronal populations and is integral to high-energy substrate oxidative metabolism within mitochondria [183]. In a preliminary study, ALCAR has been reported to reduce HIV-associated peripheral neuropathy as it leads to morphological regeneration of cutaneous nerves [184, 185]. N-acetyl-cysteine has also been shown to have a motor and sensory neuroprotective capacity. NAC has some cell-cycle regulatory potential as well as antioxidant properties and it also exerts complex effects on neurotrophic factor signalling pathways within neurons, such as blocking activation of JNK in trophic-deprived PC12 cells and uncoupling NGF activation of MAPK from that of Ras [186, 187]. Glutathione depletion, particularly intramitochondrial, increases the susceptibility of neurons to a variety of toxic stimuli like trophic factor withdrawal and oxidative stress [188]. However, N-acetyl-cysteine stimulates the synthesis of glutathione which is the principal renewable free radical scavenger within neurons. Unlike glutathione, cysteine is the rate-limiting precursor and can readily be taken up as NAC which crosses the blood-brain barrier, hence also have the advantage to be used as a therapeutic agent [189].

3.8. Ischaemic Stroke

The global root of mortality and persisting illness is the ischemic stroke and till now, no effective therapy is available for the treatment of cerebral ischemia. Recombinant plasminogen activator is the sole medicament utilized clinically and its use is restricted only to meager populations [190]. The prehistoric practice of therapeutics has given an account of plant-derived drugs for the cure of numerous disorders. In the immediate past, they have earned profuse approval due to its cost-effectiveness, appreciably higher therapeutic window and infrequent side effects. For prophylactic management of stroke, they are promising candidates. According to Siesjo *et al.*, several pathways form high volumes of free radicals during ischemia/reperfusion eventually leading to the death of cell. This state accompanied by the decreased antioxidant defence, triggers oxidative stress which plays a critical role in the pathogenesis of neuronal injury linked to stroke. The recovery of brain damage after ischemia/reperfusion through inhibition of ROS gushes is the focus of present-day in order to develop new strategies for overcoming damage provoked by stroke [191].

Withania somnifera popularly recognized as 'Aswagandha' is a neuroprotective herb used in disorders of CNS [192]. Withanolides are the active principles of *Withania somnifera*. When administered repeatedly, they have exhibited amplification in the expression of the antioxidant enzymes [193]. Flavonoids from *Scutellaria baicalensis* have shown a substantial protective effect against cerebral ischemia and ischemia/reperfusion-induced brain injury. The fundamental mechanism behind the protective effect of *Scutellaria baicalensis* flavonoids is the scavenging potential of free radicals. There has been also a reduction in MDA level in injured brain tissues and enhanced SOD enzyme activity in brain tissues after cerebral hypoxia [183, 194]. Carnosic acid (CA) is a constituent of rosemary herb. It is acquired from *Rosmarinus officinalis*. CA may correspond to a novel kind of neuroprotective electrophilic compound as it is able to cross the blood-brain barrier and move into the brain, up-

surges the concentration of reduced glutathione *in-vivo*, and protects the brain against ischemia/reperfusion brain injury using middle cerebral artery occlusion (MCAO) model [195]. The active principle ginsenosides of *Panax ginseng* reside in its root. By provoking endogenous neural stem cells activation, ginsenosides total saponins (GTS) can help in the recovery of neurological insufficiencies after focal cerebral ischemia. Thus, they boost restoration of the adult central nervous system [196]. A chemical compound isolated from the traditional Chinese herb known as ginseng 20(S)-GinsenosideRg reduces lipid peroxides, scavenges free radicals and boosts energy metabolism. In a rat model, these biological effects of ginseng 20(S)-GinsenosideRg exert neuroprotection against the cerebral ischemia brain injury [197].

A traditional Chinese herb extensively employed in the clinical treatment of stroke is *Ginkgo biloba*. Its standard extract EGb761 has exhibited substantial therapeutic outcomes on ischemic stroke. The likely reason behind it is believed to be activation of Akt–cyclic AMP-responsive element binding protein 1-Brain-derived neurotrophic factor (Akt-CREB–BDNF) pathway [198]. It has shown an improvement in behavioural neurologic outcome. The resultant neuroprotection can be ascribed to the shrinkage of brain infarct volume induced by perpetual and temporary middle cerebral artery (MCA) obstruction [199].

Acanthopanax polysaccharides are extracted from the root of *Acanthopanax senticosus*. They are comprised of chiiisanoside, eletheroside, saponin, senticoside, syringin, triterpenic and flavone compounds [200]. They have been reported to possess a wide variety of effects like anti-histaminic, antioxidant, anti-stress, hypolipidemic, immunomodulatory and sedative [201, 202]. The symptoms induced by cerebral ischemia/reperfusion injury in rat model can be improved by the treatment with Acanthopanax polysaccharides. They can also reduce the water content of the brain and infarct volume. In the brain tissue of rats with the cerebral ischemia/reperfusion injury, a decline in MDA, IL-1 and TNF- α levels with subsequent elevation of SOD and GSH-Px activities and IL-10 level has been reported after the supplementation with Acanthopanax polysaccharides [201]. Cinnamophilin (sequestered from *Cinnamomum philippinense*) and curcuma oil (isolated from powdered rhizomes of *Curcuma longa* Linn.) [203] when administered prior to cerebral ischemia has demonstrated neuroprotective effects but the underlying targets and mechanisms have not been completely understood [204].

Honokiol, a constituent of the herb *Magnolia officinalis*, can reduce the production of synaptosomal reactive oxygen groups, decrease infarct volume and attenuate Na⁺, K⁺-ATPase, mitochondrial membrane potential, mitochondrial metabolic activity in mice before and after stimulation of the brain ischaemia with middle cerebral artery occlusion. For the patients who experience ischaemic stroke, honokiol epitomizes as an encouraging therapy [205]. A common secondary effect often appearing after stroke is dementia. Primarily, there is formation and accumulation of β -amyloid that lead to progressive neuronal apoptosis. One of the phenolic phytochemicals, paeonol isolated from the Chinese herb *Paeonia suffruticosa* protects the memory loss resulting from cerebral ischemia. Paeonol treatment resulted in the

reduced level of amyloid precursor protein (APP), β -secretase enzyme immunopositive cells and apoptosis [206]. A study conducted by Hsieh, *et al.*, [207] revealed that paeonol lessens neuro-insufficiency and reduces cerebral infarction in rat model. It has also shown to complicate microglia activation and IL-1 besides scavenging superoxide anion in ischemia/reperfusion injury in rat brain. Based on the *in-vitro* studies, the methanolic extract of *Uncaria rhynchophylla* has reported to inhibit nitric oxide (NO) and TNF- α production in BV-2 mouse microglial cells. The ischemic induction of COX-2 expression and the death of CA1 neurons in hippocampus, after global ischemia have also been prevented. These findings imply that in neuroprotective activities, there is the contribution of anti-inflammatory effects [208]. Another natural compound Hydroxysafflor yellow A (HSYA) isolated from the flower of the *Carthamus tinctorius* (safflower plant), has been shown to reduce apoptosis partially *via* PI3K/Akt/GSK3 β signalling pathway in rats pointing to the fact that HSYA protects against cerebral ischaemia/reperfusion injury [209]. Hydroxysafflor yellow B (SYB) has also exhibited neuroprotective actions by recuperating the energy metabolism, scavenging free radicals and decreasing lipid peroxides in the brain tissue [210].

Rhizoma Pinelliae pedatisectae is a Chinese herbal medicine which is a dried tuber of *Pinellia pedatisecta* Schott. It has a neuroprotective action against various disorders, therefore we further investigated the effects of n-butyl alcohol extracts of *Rhizoma Pinelliae* pedatisectae against cerebral ischemic/reperfusion injury using middle cerebral artery occlusion (MCAO) ischemic rat model. The extract of *Rhizoma Pinelliae* pedatisectae exhibited protective action in a dose-dependent manner and reported to enhance antioxidant enzyme, superoxide dismutase (SOD) activity and reduce malondialdehyde (lipid membrane damage marker/oxidative stress marker), and other inflammatory markers such as TNF- α and IL-1 β . Cerebral ischemic/reperfusion injury normally leads to apoptotic neuronal cell death and prophylaxis treatment with n-butyl alcohol extracts of *Rhizoma Pinelliae* pedatisectae that reduced neuronal cell death as shown by increased Bcl-2 (anti-apoptotic marker) and decreased Bax (apoptotic marker). Thus, *Rhizoma Pinelliae* pedatisectae extract exhibited neuroprotective effects against cerebral ischemia in MCAO rat model by ameliorating oxidative stress, inflammatory and apoptotic responses [211].

A natural compound, 11-keto- β -boswellic acid, was isolated from the plant extract of *Boswelliaserrata*. Oxidative stress plays a key role in the cerebral ischemic injury. 11-keto-beta-boswellic acid is reported to be an activator of Nrf-2 which is a transcription factor that gets activated in oxidative stress and regulates detoxification pathway. Post-treatment with 11-keto- β -boswellic acid in MCAO rat model for cerebral ischemia suppressed the cerebral infarction as well as apoptotic neuronal cell death. It also reduced MDA level, alleviated SOD activity and enhanced protein expression of Nrf-2 and hemeoxygenase-1 (HO-1) in the brain. 11-keto- β -boswellic acid exerts neuroprotective effects against cerebral ischemia by alleviating oxidative stress through modulating Nrf-2/HO-1 axis pathway [212].

Osthole is a plant-derived bioactive coumarin compound which is found to be present in various plants such as

Table 7. Functions of constituents of natural products for ischaemic stroke.

S.No.	Natural Products-Ischemic Stroke	Common Name	Constituent	Functions	Refs.
1	<i>Acanthopanax senticosus</i>	Devil's bush	Acanthopanax polysaccharides	Lowering of brain water content and infarct volume	[200, 201]
2	<i>Cinnamomum philippinense</i>	Philippine cinnamon	Cinnamophilin	Neuroprotection	[107, 202]
3	<i>Curcuma longa</i>	Turmeric	Oil isolated from powdered rhizomes	Neuroprotection	[203]
4	<i>Ginkgo biloba</i>	Maidenhair tree	Extract EGb761	Launch of Akt-CREB-BDNF pathway	[197]
5	<i>Ginseng/ Panax ginseng</i>	Five fingers/ Radix ginseng	20(S)-GinsenosideRg/ Ginsenosides	Hunting of free radicals, energy metabolism rejuvenation/ Trigger of endogenous neural stem cells activation	[195, 196]
6	<i>Magnolia officinalis</i>	Houpou	Honokiol	The decline in production of synaptosomal reactive oxygen groups	[204]
7	<i>Paeonia suffruticosa</i>	Tree peony	Paeonol	Protection of memory loss developing from ischemia of the brain	[205, 206]
8	<i>Rosmarinus officinalis</i>	Rosemary	Carnosic acid	Improvements in reduced glutathione concentration	[194]
9	<i>Carthamus tinctorius</i>	Safflower	Hydroxysafflor yellow A (HSYA) Hydroxysafflor yellow B (SYB)	Protection in response to cerebral ischaemic reperfusion injury	[208]
10	<i>Scutellaria baicalensis</i>	Baikal skullcap	Flavonoids	Eradication of free radicals	[193]
11	<i>Withania somnifera</i>	Ashwagandha	Hydroalcoholic extract	Augmentation in the antioxidant enzyme expression	[191]
12	<i>Rhizoma Pinelliae pedatisectae</i>	Pinellia tuber	n-butyl alcohol extract of tuber	Enhanced antioxidant enzyme, suppressed inflammatory and apoptotic responses	[210]
13	<i>Boswellia serrata</i>	Indian Olibanum, Indian Frankincense	11-keto- β -boswellic acid	Modulator of Nrf-2/HO-1 pathway	[211]
14	<i>Cnidium monnieri</i>	Monnier's snowparsley	Osthole	Regulate apoptosis pathway	[212]
15	<i>Coffee, Tea, Fruits & Vegetables</i>	—	<i>Caffeic acid</i>	Inhibit lipoxygenase enzyme, modulate oxidative stress	[221]

Cnidium monnieri. Pretreatment with osthole has been shown to exert neuroprotective effects against cerebral ischemia-reperfusion injury in MCAO rat model. Osthole protects the brain tissue against cerebral ischemia-reperfusion injury as shown by histological analysis and cerebral function. Moreover, osthole also reduced Bax and activated caspase-3 as well as enhanced Bcl-2 protein expression in the brain tissue along with a reduced number of apoptotic cells. Thus, osthole exhibited neuroprotective action against cerebral ischemia due to its anti-apoptotic effects [213].

Caffeic acid is a natural compound present in several products such as tea, coffee, fruits and vegetables. It has various biological properties like anti-oxidant, anti-microbial, anti-inflammatory, etc. It was reported that the inhibition of 5-

lipoxygenase (LOX) enzyme has been shown to protect the brain from ischemic injury in a rat model. Caffeic acid, an inhibitor of LOX enzyme, has been shown neuroprotective effects against global cerebral ischemia-reperfusion injury using bilateral carotid artery occlusion (BCAO) rat model. Treatment with caffeic acid suppressed the escape latency performed for spatial learning and memory using Morris water maze. Caffeic acid treatment reduced hippocampus neuronal damage, increased number of neuron, reduced NF- κ B expression as well as MDA level, and enhanced SOD activity in the hippocampus region of the brain. Treatment with caffeic acid significantly decreased LOX expression, thus caffeic acid exhibited neuroprotective effects mainly through LOX inhibition [214] (Table 7).

CONCLUSION

This review summarizes that the facts are comprehensive and deeply informative about the various established activities of natural products in *in vitro* and *in vivo* preclinical models, and their potential neuro-therapeutic applications using the available knowledge in the literature. Therefore, this review would assist as a reference for current advances in the study on natural products for neuroprotective.

LIST OF ABBREVIATIONS

3-NP	=	3-nitropropionic acid	GSK3 β	=	Glycogen synthase kinase 3 beta
ACh	=	Acetylcholine	GTS	=	Ginsenosides Total Saponins
AChE	=	Acetylcholine Esterase	HD	=	Huntington's Disease
AD	=	Alzheimer's Disease	HIV	=	Human Immunodeficiency Virus
AED	=	Anti-Epileptic Drugs	HSYA	=	Hydroxysafflor Yellow A
Akt	=	Protein kinase B	IFN- γ	=	Interferon gamma
ALCAR	=	Acetyl-L-Carnitine	IGF	=	Insulin-like Growth Factor
APP	=	Amyloid Precursor Protein	IL-1	=	Interleukin-1
APP	=	Amyloid Precursor Protein	iNOS	=	Inducible Nitric Oxide Synthase
BACE	=	Beta-site APP Cleaving Enzyme	JNK	=	c-Jun amino-terminal Kinase
BAD	=	Bcl-2-Associated Death promoter	L-DOPA	=	Levo-dihydroxyphenylalanine
Bax	=	Bcl-2-like protein 4	LD	=	Lethal Dose
Bcl-2	=	B-cell lymphoma-2	LDH	=	Lactate Dehydrogenase
Bcl-W	=	Bcl-2-like protein	MAO	=	Monoamine Oxidase
Bcl-xL	=	B-cell lymphoma-extra-large	MAPK	=	Mitogen-Activated Protein Kinase
BDNF	=	Brain Derived Neurotrophic Factor	MeSH	=	Medical Subject Heading
BIM	=	Bcl-2-like protein 11	MCA	=	Middle Cerebral Artery
BM	=	<i>Bacopa monnieri</i>	MDA	=	Malondialdehyde
BMP	=	<i>Petasites japonicum</i>	MES	=	Maximal Electroshock
CA	=	<i>Cornuammonis</i>	MID	=	Multi-Infarct Dementia
CA	=	Carnosic acid	MPTP	=	1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine
CK	=	Creatine Kinase	NAC	=	N-Acetyl-Cysteine
CNS	=	Central Nervous System	NF- κ B	=	Nuclear Factor-kappa B
COX-2	=	Cyclooxygenase-2	NGF	=	Nerve Growth Factor
CREB	=	cAMP Response Element Binding protein	NO	=	Nitric Oxide
DA	=	Dopamine	OS	=	Oxidative Stress
DOPA	=	Dihydroxyphenylalanine	PD	=	Parkinson's Disease
ER	=	Estrogen Receptor	PI3K	=	Phosphoinositide 3-Kinase
ERK	=	Extracellular signal-Regulated Kinases	PNS	=	Peripheral Nervous System
FAO	=	Food and Agriculture Organisation	PTZ	=	Pentylentetrazole
GABA	=	Gamma aminobutyric acid	Ras	=	Retrovirus-Associated DNA Sequences
GPED	=	G Protein-Coupled Estrogen Receptor	ROS	=	Reactive Oxygen Species
GSH-Px	=	Glutathione peroxidase	SD	=	Sprague Dawley
			SDH	=	Succinic Acid Dehydrogenase
			SN	=	Substantia Nigra
			SOD	=	Superoxide Dismutase
			SYB	=	Hydroxysafflor Yellow B
			THLE	=	Tonic Hind Limb Extensor
			TNF	=	Tumor Necrosis Factor

TUNEL	=	Terminal deoxy nucleotidyl transferase-mediated dUTP-biotin nick end labelling
VGSC	=	Voltage-Gated Sodium Channel
WHO	=	World Health Organization

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

This work is supported by SERB, Department of Science and Technology, Grant No. YSS/2015/001851 and SR/NM/NB-1044/2016(G). Anas Ahmad is thankful to INST for providing fellowship.

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