

Review Article

PROMISING NEUROPROTECTIVE PLANTS FROM NORTH-EAST INDIA

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ABSTRACT

Neuroprotection is a broad term commonly used to refer therapeutic strategies that can prevent, delay or even reverse neuronal damage. Herbal medicines are widely used across the globe as economical, effective and safer alternative remedies. North-East (NE) India harbours a large number of medicinal plants, it falls under Indo-Burma global hotspot one of the 34 global biodiversity hotspots. In traditional practice of medicines, people here uses a variety of medicinal plants for the treatment of various ailments. The purpose of this manuscript is to review the plants with neuroprotective potential from NE India and to provide the reference for future study of new and alternative remedies for the treatment of neurological ailments.

Keywords: Neuroprotection, North-East India, Herbal Medicine, Neurotoxicity, Neuroprotective plant.

INTRODUCTION

The North-east (NE) India is one of the richest in biological values, high in endemism and holds a large number of rare species that are now under serious threat. NE India is the eastern-most region of India connected to the main land India via a narrow corridor present between Nepal and Bangladesh. The region comprises of eight states: Arunachal Pradesh, Assam, Manipur, Meghalaya, Mizoram, Nagaland, Sikkim and Tripura and is endowed with a wide range of physiographic and eco-climatic conditions. NE India falls under Indo-Burma global hotspot one of the 34 global biodiversity hotspots recognized currently (2005). The WWF has identified the Entire Eastern Himalaya as a priority Global 200 Eco-region.

The nervous system is a complex network of nerve cells, which regulates body's voluntary and involuntary actions and transmits nerve impulses between different parts of the body. It consists of two main parts, the central nervous system (CNS) which consists of the brain and the spinal cord and the peripheral nervous system (PNS) which is the rest of the nervous system structures that do not lie within the CNS. Chemically, the brain and spinal cord is isolated by the so-called blood-brain barrier, which prevents most types of chemicals from moving from the bloodstream into the interior of the CNS. These protections make the CNS less susceptible in many ways than the PNS.

Mechanisms of neurotoxicity

Amyloid cascade hypothesis

The amyloid cascade hypothesis has dominated the field of Alzheimer's disease (AD) research and has provided the intellectual framework for therapeutic intervention [1]. It proposes that the deposition of β -amyloid is the initial pathological event in AD leading to the formation of senile plaques and then to neurofibrillary tangles, neuronal cell death, and ultimately dementia. Genetic studies identified that mutations in the amyloid precursor protein, presenilin 1, and presenilin 2 genes leading to the accumulation of β -amyloid and early-onset familial dementia [2].

Apoptosis

Apoptosis or programmed cell death (PCD) is a cascade of cellular events leading to characteristic morphological changes in cells and then death.

The changes include cell shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA fragmentation. Caspase-3 has been identified as a key mediator of neuronal PCD. This protease plays a central role in the developing nervous system and its activation is observed early in neural tube formation and persists during postnatal differentiation of the neural network. Caspase-3 activation, a crucial

event in neuronal cell death program, is also a feature of many chronic neurodegenerative diseases [3].

Excitotoxicity

This concept was formulated in 1978 by Olney. Excitotoxicity is neuronal degeneration caused by over-stimulation of the glutamate receptors. During glutamatergic neurotransmission, glutamate released from the presynaptic neuron activates ionotropic glutamate receptors such as the N-methyl-D-aspartate receptor (NMDA) and AMPA receptor present on the post synaptic neurons. Activation of these glutamate receptors results in the influx of Na^+ and Ca^{2+} ions into the cell, leading to depolarization and ultimately to the generation of an action potential [4]. Although glutamate plays a central role in excitatory neurotransmission, alterations in glutamate homeostasis can have significant repercussions on neurons through the generation of neurotoxic or excitotoxic cascades [5]. Continuous activation of large numbers of NMDA receptors leads to increases in intracellular calcium loads and catabolic enzyme activities, which can trigger a cascade of events eventually leading to apoptosis or necrosis [6]. Experimental evidences support that excitotoxicity could contribute to neuronal damage in stroke, neurotrauma, epilepsy, and a number of neurodegenerative disorders including amyotrophic lateral sclerosis [7].

Oxidative stress

Oxidative stress, defined as a disturbance in the balance between the productions of reactive oxygen species (ROS) and antioxidant defenses. Due to oxidative stress over accumulation of ROS occurs, excessive ROS result in severe deleterious effects on cells. ROS mediate lipid peroxidation (LPO). LPO is a self-sustaining process, which amplifies the effects of the original free radical and leads to the activation of a cascade of toxic reactions resulting in extensive tissue damage. The brain is particularly susceptible to LPO since the composition of neuronal tissue makes the brain vulnerable to chain reactions mediated by free radicals and leading to products of LPO. The brain contains high levels of polyunsaturated fatty acids and high levels of redox transition metal ions in addition to its high oxygen consumption. On the other hand, levels of lower molecular weight and enzymatic antioxidants are relatively low and might contribute to the accumulation of oxidative damage [8]. LPO in the brain is one of the major factors of several neurological disorders.

Proinflammatory cytokines

Microglia gets activated in response to a number of different pathological conditions within the CNS including injury, ischemia, and infection. Microglial activation results in their production of pro-

inflammatory cytokines such as Interleukin-1 (IL-1), IL-6, and Tumor necrosis factor alpha (TNF- α). While release of these factors is typically intended to prevent further damage to CNS tissue, they may also be toxic to neurons and other glial cells. Short-term microglial activity is generally accepted to serve a neuroprotective role, chronic activation has been implicated as a potential mechanism in neurodegenerative disorders. Mounting evidence indicates that chronic microglial activation may also contribute to the development and progression of neurodegenerative disorders. Unfortunately, determining the role of pro-inflammatory cytokines in these disorders has been complicated by their dual roles in neuroprotection and neurodegeneration [9].

Cholinergic theory

The cholinergic hypothesis is one of the leading hypothesis for the neurochemical basis of AD. The Hypothesis suggests that degeneration of cholinergic neurons in the basal forebrain and the associated loss of cholinergic neurotransmission in the cerebral cortex and other areas contributed significantly to the deterioration in cognitive function seen in patients with AD [10].

Neuroprotection

Neuroprotection is a broad term commonly used to refer to any type of therapeutic strategy, usually pharmacological, that can prevent, delay or even reverse neuronal damage, whether it be neuronal death, axonal degeneration or any other form of neuronal injury. Neuroprotective strategies presently being evaluated include acetylcholinesterase inhibitor, glutamate antagonists, calcium channel blockers, nitric oxide synthase inhibitors etc.

Herbal protection

Herbs can be used as an alternative remedy for different neurological disorders. Different bioactive compounds isolated from herbs are being successfully used for the treatment of neurological disorders. Due to the side effects of chemical drugs, herbal remedies are gaining popularity. Several scientific studies reveal that herbal extracts and active constituents isolated from different herbs can ameliorate nerve disorders, improve learning and memory.

Acorus calamus l

Acorus calamus L. (AC) which is also known as Sweet flag (English), Bach (Assamese) is herbaceous perennial aromatic herb belonging to the family Acoraceae. AC roots and rhizomes have been used in Indian system of traditional medicine for the hundreds of years and it is highly valued as a rejuvenator for the brain and nervous system and as a remedy for digestive disorders. Recently it is scientifically proved that AC rhizome constituents, particularly α and β -asarone, possess a wide range of pharmacological activities such as sedative, CNS depressant, behavior modifying, anticonvulsant, acetylcholinesterase (AChE) inhibitory and memory enhancing activities [11,12]. AC is registered in the Pakistani Materia Medica where both the roots and rhizomes are used for nervous diseases and disorders, whereas the rhizome is especially indicated in cases of neurological symptoms of the brain [13]. AC also shows neuroprotective effect against stroke and chemically induced neurodegeneration in rats [14,15].

Asparagus racemosus wild

Asparagus racemosus Wild. (AR) belong to the family Asparagaceae. It is also called as Satmuli (Hindi), Satumul (Assamese). It is a well-known Ayurvedic rasayana which prevent ageing, increase longevity, impart immunity, improve mental function, vigor and add vitality to the body. It is also used in nervous disorders, dyspepsia, tumors, inflammation, neuropathy and hepatopathy [16]. The major active constituents of AR are steroidal saponins (shatavarins I-IV), isoflavones, asparagine, racemosol, polysaccharides, mucilage, vitamins A, B₁, B₂, C, E, Mg, P, Ca, Fe, and folic acid present in roots. Other primary chemical constituents of AR are essential oils, asparagine, arginine, tyrosine, flavonoids (kaempferol, quercetin, and rutin), resin, and tannin [17, 18]. Reports indicate that the pharmacological activities of AR root extract include antiulcer [19], antioxidant [20], anti-diarrheal [21], anti-diabetic and immunomodulatory activities [22]. Methanolic extract administered

to mice significantly decreased brain Monoamine Oxidase A (MAO-A) and Monoamine Oxidase B (MAO-B) activity levels it has been found that the methanolic extract possesses antidepressant activity probably by inhibiting MAO-A and MAO-B, and through interaction with adrenergic, dopaminergic, serotonergic and GABAergic systems (Gamma amino butyric acid) [23]. Methanolic extract of AR also significantly inhibited cholinesterase and act as a non-selective competitive inhibitor as compared hexane and chloroform extracts [24]. A study on kainic acid induced hippocampal and striatal neuronal damage in mice treated with methanolic root extract showed an enhancement in glutathione peroxidase activity, glutathione content, reduction in membrane LPO and protein carbonyl in brain impaired by kainic acid. They concluded plant extract plays the role of an antioxidant by attenuating free radical induced oxidative damage. The oxidative damage protection of the hippocampal and striatal regions of the brain is useful in the neurodegenerative disease [25]. Another study by Laddawan Lalert *et al.* on neuroprotective effects of the AR root extract on ovariectomized rats demonstrated that AR may be a beneficial agent for prevention of cognitive decline induced by ovariectomy [26].

Bacopa monnieri (L.) wettst

This plant belongs to family Plantaginaceae. This medicinal plant is locally known as Brahmi. The name Brahmi is derived from the word 'Brama' the mythical "creator" in the Hindu pantheon [27]. *Bacopa monnieri* (L.) Wettst. (BM) is extensively used since times immemorial in traditional Indian medicine as a nerve tonic and thought to improve memory [28]. Several studies suggest that BM is a potential cognitive enhancer and neuro protectant [29]. The chemical constituent responsible for the effect of BM on learning schedules was identified as a mixture of two saponins designated as bacosides A and B. They also enhanced protein kinase activity and produced an increase in protein in hippocampus [30]. BM extract protects against AD, it protects neurons from beta-amyloid-induced cell death. This neuroprotection is due to its ability to suppress neuronal oxidative stress and the AChE activity [31].

Celastrus paniculatus Wild

Celastrus paniculatus Wild. (CP) belongs to family Celastraceae. It is commonly known as Jyotishmati, Pokitai (Assamese). In traditional system of medicine Ayurveda, Unani CP was used to treat physical weakness, mental confusion, alleviate asthma symptoms, reduce headaches, cure joint pain, arthritis and it was also administered as a powerful brain tonic, appetite stimulant, and emetic [32]. Phytochemical studies show the presence of evonoinoate, sesquiterpene, alkaloids paniculatin A, paniculatin B and wifornine F, celastrine, celapanine, celapanigine, celapagine, polyalcohol (malangunin, malkanginnol, malkanguniol and paniculatadiol), triterpenoids (pristimerin), sterols (β - amyryn and β -sitosterol) [33-35]. Pre-treatment of neuronal cells with CP seed oil significantly attenuated glutamate-induced neuronal death. CP seed significantly and reversibly inhibited whole-cell currents activated by N-methyl- D-aspartate. The results suggest that water soluble extracts of CP seed (CPWSE) protected neuronal cells against glutamate induced toxicity by modulating glutamate receptor function. CPWSE (200 mg/kg body wt. for 14 days) showed an improvement in learning and memory in both the shuttle-box and step-through paradigms. 100, 200 and 300 mg/kg body wt. doses of the aqueous extract increased the number of avoidances in the shuttle-box and step-through latency the in step-through apparatus. The 200 and 300 mg/kg body wt. doses of aqueous extract showed a significant increase in step-down latency. Only 200 and 300 mg/kg body wt. stimulated a significant decrease in the brain levels of malondialdehyde (MDA), with simultaneous significant increases in levels of glutathione and catalase [36].

Centella asiatica (L.) Urb

Centella asiatica (L.) Urb. (CA) has been valued for centuries in Ayurvedic medicine. It is commonly known as Manimuni (Assamese), Indian pennywort (English). CA belongs to the family of Apiaceae. The scientific studies have reported a variety of biochemical components in CA which include flavonoids, terpenoids, essential oils, alkaloids, carbohydrates, amino acids etc. [37,38].

Since the ancient time, CA is used to enhance intelligence and improve cognitive function. And now it is experimentally proved in 28 human samples that CA enhance working memory and improve self-mood [39]. Asiatic acids isolated from CA showed enhanced learning and memory properties in male Sprague–Dawley rats [40]. It also showed to improve brain function in juvenile and young mice when aqueous extract of CA is administered at a dose of 200 mg/kg [41]. One of the major findings of CA is that it can inhibit AChE, the hydro alcoholic extract of the plant was tested *in vitro* against AChE, which is the key enzyme in the pathogenesis of AD. Since deficit in the level of acetylcholine (ACh), which is hydrolyzed by AChE, has been identified in the brains of AD patients, inhibition of AChE as well as its sister enzyme butyrylcholinesterase (BChE) has become a rational target for drug development against AD [42]. The extract was found to inhibit AChE with 50% of inhibition rate at 150 µg/mL concentration by the spectrophotometric method of Ellman [43]. *In vivo* studies in rats, have shown evidence that CA has a remarkable antioxidant effect and has the potential to decrease in MDA and an increase in glutathione and catalase levels. In addition to neuroprotective effect of CA, it has been reported to own a wide range of biological activities such as wound healing [44], anti-inflammatory [45], antipsoriatic [46], antiulcer [47], hepatoprotective [48], anticonvulsant [49], sedative [50], immunostimulant [51], cardioprotective [52], antidiabetic [53], cytotoxic and antitumor [54], antiviral [55], antibacterial [56], insecticidal [57], antifungal [58], antioxidant [59], and for leprosy [60] and venous deficiency treatments [61].

***Coriandrum sativum* L**

Coriandrum sativum L. (CS) belongs to family Apiaceae is highly reputed ayurvedic medicinal tree commonly known as the Dhanya. In Indian traditional medicine, coriander is used in disorders of digestive, respiratory and urinary system [62]. CS has been reported to exhibit several pharmacological effects such as antioxidant activity [63] anti-diabetic activity [64], anti-mutagenic activity [65], antihelmintic activity [66], sedative-hypnotic activity [67], anticonvulsant activity [68], diuretic activity [69], cholesterol lowering activity [70], antifungal activity [71], anti-feeding activity [72], anticancer activity [73], anxiolytic activity [74], hepatoprotective activity [75], anti-protozoal activity [76], anti-ulcer activity [77], post-coital anti-fertility activity [78], heavy metal detoxification [79]. A study by Mahendra and Bisht observed that the extract of 100 and 200 mg/kg produced anti-anxiety effects similar to diazepam [80]. Pretreatment with methanolic extract of leaves of CS (200 mg/kg) for 15 days increased endogenous enzyme levels of superoxide dismutase, glutathione, catalase and total protein levels, and reduces cerebral infarct size, LPO and calcium levels in experimental rat. It also attenuated reactive changes in brain histology like gliosis, lymphocytic infiltration and cellular edema [81]. Another study by Vasudevan Mani & Milind Parle in rat showed that leaves of CS (5, 10 & 15 % W/W of diet) produced a dose dependent improvement in memory scores of young as well as aged rats. Leaves of CS also reversed successfully the memory deficits induced by scopolamine (0.4 mg/kg, i. p.) and diazepam (1 mg/kg, i. p.). Cholesterol-lowering, anti-inflammatory and antioxidant properties of leaves of CS may favorably contribute to its memory-enhancement effect [82].

***Crocus sativus* L**

Crocus sativus L. (CS) belongs to family Iridaceae. The dried red stigma of CS is a variety of spice commercially named as Saffron. The stigmas of the plant are used for they contain a variety of chemical constituents like the crocetin, crocin and other flavonoids which make them suitable to possess diversified medicinal properties for treating various ailments [83]. CS has been traditionally used as an acrid, aphrodisiac, analgesics, anodyne, antispasmodic, bitter, cephalgia, diuretic, depression, epilepsy, fragrant, fever, galactagogue, inflammations, laxative, stimulant, stomachic and as a tonic [84]. Scientific studies showed that CS also possesses a number of therapeutic activities such as antihypertensive, anticonvulsant, antitussive, antigenotoxic, anticancer, cytotoxic effects, anxiolytic, antioxidant, antidepressant, anti-inflammatory, and relaxant activity [85]. Aqueous extract of CS was reported to improve

ethanol-induced impairments of learning behavior in mice and ethanol-induced inhibition of hippocampal long-term potentiation, a form of activity-dependent synaptic plasticity that may underlay learning and memory [86]. Abdullah Shafique Ahmad *et al.* evaluated the Parkinsonism on the rat model to check the neuromodulatory effects of crocetin in a 6-hydroxydopamine. The results showed that crocetin could prevent the Parkinsonism as well as the neurological disorder [87]. The water: methanol (50:50, v/v) extract of CS stigmas inhibited A-beta fibrillogenesis, formed by oxidation of the amyloid beta-peptide fibrils in AD, in a concentration and time dependent manner at lower concentrations than it's another constituent dimethylcrocetin [88]. Anxiety is an atypical sense of fear and apprehension due to tension, increased pulse, sweating etc. It is also an unpalatable state of inner turmoil. Rat models were used in the study to check the anxiolytic properties in the presence of crocin and the authors N. Pitsikas *et al.*, found that the crocin which is the active constituent of CS. Possess the anxiolytic-like effects in the rat [89].

***Clitoria ternatea* L**

Clitoria ternatea L. (CT), is a herbaceous medicinal plant commonly known as Aparajit (Hindi), Aparajita (Assamese). CT belongs to family Leguminosae. Traditionally in Ayurvedic medicine, it has been used for centuries as a memory enhancer, nootropic, antistress, anxiolytic, antidepressant, anticonvulsant, tranquilizing and sedative agent. A wide range of secondary metabolites including triterpenoids, flavonol glycosides, anthocyanins and steroids has been isolated from CT. Scientific studies has reconfirmed that its extracts possess a wide range of pharmacological activities including antimicrobial, antihelmintic, antipyretic, proteolytic, anti-inflammatory, larvicidal, analgesic, diuretic, local anesthetic, antidiabetic, insecticidal, and vascular smooth muscle relaxing properties [90]. Oral intubation with 100 mg/kg of aqueous root extract of CT for 30 days has proved to improve learning and memory in rats. Further work on the dendritic arborization of CA3 pyramidal neurons in the hippocampi of rats showed significant increase in apical and basal dendritic branches [91]. Intraperitoneal administration of alcoholic extract of CT to rats and mice has been reported to produce sedation and diminished alertness [92]. Oral treatment with alcoholic extracts of aerial and root parts of CT has been reported to increase ACh content and AChE activity in the rat brain and improve memory retention. Intellect promotion and memory retention may be related to effects on cholinergic activity in the CNS as some studies have shown. A study investigating both the aerial parts and roots of CT showed alcoholic root extracts to be more effective in attenuating memory deficits in rats compared to aerial parts. Enhanced memory retention following oral administration of the CT root extract was associated with increased levels of ACh and choline acetyltransferase in rat brain, but any relationship with inhibition of AChE activity was not established, and cortical AChE activity was actually found to be increased [93]. An aqueous extract of the root also increased ACh levels in rat hippocampus following oral administration, and it was hypothesised that this effect may be due to an increase in ACh synthetic enzymes [94].

***Curcuma longa* L**

Curcuma longa L. (CL) is a member of the ginger family, Zingiberaceae and is thought to be indigenous to the Indian subcontinent. It is also called as Haldi. Indigenous systems of medicine, including the Ayurvedic systems, have widely used turmeric for centuries in the treatment of many inflammatory conditions and diseases such as biliary disorders, anorexia, cough, diabetic wounds, hepatic disorders, rheumatism and sinusitis [95]. The active constituents of CL are the flavonoid curcumin and various volatile oils, including tumerone, atlantone, and zingiberene. Other constituents include sugars, proteins, and resins [96]. Curcumin passes the blood brain barrier. 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 [97]. Some compounds from CL, including curcumin, demethoxycurcumin, bisdemethoxycurcumin and calebic-A and some of its synthetic analogues, were shown to protect PC12 cells

from β -amyloid insult in vitro, this activity was also suggested to be due to an antioxidant effect [98]. Pretreatment of cells with an aqueous extract of CL (0.5-microgram/ml) prior to hydrogen peroxide (H_2O_2) exposure significantly prolonged cell survival, increased antioxidant enzyme activity and decreased MDA concentration. Another activity, that is perhaps relevant to the management of symptoms of cognitive-related disorders, is antidepressant activity. An aqueous extract of CL demonstrated antidepressant activity in mice following oral administration, which was associated with inhibition of brain MAO-A [99]. Animal research demonstrated that curcumin limits ischemia-reperfusion damage in the heart and brain [100,101]. Curcumin protects the brain against damage caused by alcohol consumption, whereby a decrease in oxidative stress and lipid peroxidation and an improvement of the glutathione level in brain tissue is seen. In healthy volunteers, a low oral dose of curcumin (20 mg per day for 75 days) resulted in a significant fall in serum LPO by 60% [102].

***Eclipta prostrata* (L.)L**

Eclipta prostrata (L.)L (EP) belongs to family Compositae. The plant is characterized by presence of array of phytochemicals including alkaloids, glycosides, coumarins, flavonoids and sterols [103]. EP has been traditionally used for blackening, promoting hair growth and strengthening the hair. In Ayurveda medicine, the leaf extract is considered a powerful liver tonic and rejuvenative [104]. Pharmacological activities of EP include analgesic activity [105], anti-aggression activity [106], anti-bacterial activity [107], anticancer activity [108], anti-diabetic activity [109], anti-helminthic activity [110], hepatoprotective activity [111], anti-inflammatory activity [112], hair growth promoter activity [113], besides these EP has nootropic potential, it enhances memory and learning [114]. Pretreatment with hydroalcoholic extract of EP significantly increases the levels of superoxide dismutase, glutathione peroxidase, reduced glutathione, catalase, glutathione-S-transferase, glutathione reductase and decrease in MDA in brain. EP at higher dose markedly reduced ischemic neuronal loss of the rat brain induced by occluding bilateral common carotid arteries for 30 min, followed by 4 h reperfusion [115].

***Enhydra fluctuans* Lour**

Enhydra fluctuans Lour. (EF) is a semi-aquatic, annual herbaceous plant, locally known as Water Cress (English), Helechi (Assamese). EF is a species common to North-Eastern India. Phytochemical analysis of the extract of EF revealed the presence of alkaloids, saponins, flavonoids, triterpenoids, steroids, tannins, carbohydrates and glycosides [116]. The plant has been used in Indian medicine in the treatment of various ailments. EF has been reported to own analgesic [117], cytotoxic [118], phagocytic [119], antidiabetic, antimicrobial [120], hepatoprotective [121], anti-inflammatory [122], antidiarrheal [123], anti-oxidant [124], anti-cancer activity [125], besides these it also possesses neuroprotective potential. Roy *et al.*, studied neuropharmacological effects of three fractions (Benzene, Chloroform and Ethyl Acetate) of aerial parts of EF using mice models on central and peripheral nervous system. Results showed significant spontaneous motility depressant, sedative, anticonvulsant and anti-stress activity [126].

***Glycyrrhiza glabra* L**

Glycyrrhiza glabra L. (GG) belongs to family Leguminosae. GG is commonly known as Yashti-madhuh, liquorice. It is reported to have antiviral [127], anticancer [128], anti-ulcer [129], anti-diabetic, antioxidant [130], immunomodulatory activity [131], antimicrobial activity [132], anti-inflammatory activity [133], anticonvulsant [134]. Glabridin, a major flavonoid of GG, possesses multiple pharmacological activities. Xue-Qing Yu *et al.* showed that Glabridin significantly attenuated the level of brain MDA induced by middle cerebral artery occlusion in rats, while it elevated the level of two endogenous antioxidants in the brain, i. e. superoxide dismutase and reduced glutathione [135]. A study by P. Muralidharan aqueous extract administration restored the decreased levels of brain enzymes such as glutamate and dopamine and decreased AChE activity significantly in hypoxic rats induced by providing sodium nitrite drinking water to rats for 14 days [136]. Dinesh Dhingra *et al.*

investigate the effects of GG on learning and memory in mice. Elevated plus-maze and passive avoidance paradigm were employed to test learning and memory. Three doses (75, 150 and 300 mg/kg) of aqueous extract of GG were administered for 7 successive days in separate groups of animals. The dose of 150 mg/kg of the aqueous extract of GG significantly improved learning and memory of mice. Furthermore, this dose significantly reversed the amnesia induced by diazepam (1 mg/kg) and scopolamine (0.4 mg/kg) [137]. A study by A. K. Teltumbde *et al.* on male students to evaluate the effect of Yashtimadhu oral supplementation on the mental intelligence and memory function. The overall Non Verbal Intelligence Test (NVIT) results indicate that oral consumption of Yashtimadhu tablets BID improves the intelligence level among the student when compared to students who received placebo treatment. In both classes, mild memory improvement with Yashtimadhu treatment was observed as compared to control students. The improvement was observed in NVIT as compared to memory was quite higher. The study concluded that Yashtimadhu consumption improves the general intelligence rather than STM (short term memory) [138].

***Huperzia serrata* (Thunb.)Trevis**

Huperzia serrata (Thunb.)Trevis. (HS) a traditional Chinese herb which is known as a Firmoss, Club moss (English), QianCeng Ta/Jin Bu Huan (Chinese) belongs to family Lycopodiaceae. It has been suggested that HS and its other allied species found in India, and a variety of species of *Huperzia* including *Huperzia serrata* is found in North-East India. HS have been used in traditional Chinese medicine for the treatments of various ailments, including contusions, strains, swellings, schizophrenia, and myasthenia gravis [139]. The phytochemical studies of *Huperzia* show chemicals like triterpenes, flavones, phenolic acids and alkaloids [140]. Recently, it has been reported that the alkaloid, Huperzine A (HupA), isolated from HS is found to be a strong AChE inhibitor and used for the treatment of AD and organophosphate poisoning in China [141,142]. In addition to cholinesterase inhibition, HupA has been demonstrated to protect against H_2O_2 and β -amyloid ($A\beta$)-induced cell lesion, decrease the level of LPO, increase antioxidant enzyme activities in rat PC12 (pheochromocytoma) and NG108-15 (neuroblastoma X glioma) cell lines and primary cultured cortical neurons and protect against serum deprivation-induced toxicity, oxygen-glucose deprivation-induced toxicity and ischemia-induced toxicity which may benefit AD [143].

***Morus alba* L**

Morus alba L. (MA), a popular medicinal plant belongs to family Moraceae, has long been used commonly in Ayurvedic and many of traditional systems of medicine. In folk medicine, mulberry leaves, root bark and twigs have long been used to reduce fever, protect the liver, improve eyesight, strengthen the joints, facilitate the discharge of urine and lower blood pressure [144]. MA contains various phytochemicals, including alkaloids, flavonoids, glycosides, terpenoids, steroids, volatile oils and tannins [145]. Several scientific studies reveal the important pharmacological activities of MA including antidiabetic [146], antihelminthic, antimicrobial [147], antioxidant [148], anxiolytic [149], immunomodulatory [150], nephroprotective [151]. Tian *et al.* reported that the neurodegeneration is mostly caused by free radical production. Neurological disorders such as Parkinson's disease (PD) and AD have been due to the depletion of GABA in the brain [152]. Kang *et al.* (2006) developed a process to increase the GABA level in MA leaves by various anaerobic treatments and they are subjected to in vitro and in vivo cerebral ischemia model. The results suggest that the anaerobic treatment of MA leaves increases the neuroprotection against in vivo cerebral ischemia as compared to in vitro [153]. In further study, it was investigated that cyanidin-3-O- β -D-glucopyranoside (C3G) was separated from MA fruit extract. C3G has neuro protective effect on cerebral ischemic damage in vivo and PC12 cells exposed to hydrogen peroxide in vitro [154]. PD is a common neurodegenerative disorder and is due to the loss of dopaminergic neurons in substantia nigra pars compacta. In vitro and in vivo studies of ethanolic extract of MA fruit was evaluated in PD models. The result showed that the antioxidant and anti-apoptotic effects of MA significantly protected neurons from neurotoxins in in vitro and in vivo models [155]. AD is another

common neurodegenerative disorder. The use of MA leaves reduced the risk of this disease and leaf extract of mulberry provides a significant source of treatment for AD by inhibition of amyloid beta-peptide fibril formation. As a result, attenuation of the neurotoxicity induced by amyloid beta-peptide was observed [156]. These studies suggested that MA or their isolated compounds can be used as neuroprotective agents for the treatment of neurodegenerative diseases.

Ocimum sanctum

Ocimum sanctum (OS), the plants of genus *Ocimum* belonging to family Labiatae are very important for their therapeutic potentials. OS, known as 'Tulsi' in Hindi and 'Holy Basil' in English and 'Tulasi' in Assamese. The plant is also reported to contain alkaloids, glycosides, saponins, tannins, an appreciable amount of vitamin C, and traces of maleic acid, citric and tartaric acid [157]. OS has been shown to possess multifarious medicinal properties such as analgesic activity [158], anti-ulcer activity [159], antiarthritic activity [160], immunomodulatory activity [161], antiasthmatic activity [162], anticonvulsant activity [163], antidiabetic activity [164], anti-inflammatory activity [165], antioxidant activity [166], anti stress activity [167]. Chatterjee *et al.* studied the effect of ethanol extract of leaves of OS in Swiss albino mice, against both anxiety and depressive disorder. Depression was studied through tail suspension test and forced swim test. Anxiety experiments included light dark test, elevated plus maze test, and hole-board test. The OS extracts show antianxiety and antidepressant properties at the same dose and can be a potential therapeutic agent against mixed anxiety and depressive syndrome. A study by Mahmood Samim *et al.* showed neuroprotective activity of OS in rotenone induced PD in Rats [168]. Another study by M. P. Venuprasad, hydroalcoholic extract of OS (OSE), the extract exhibited strong antioxidant activity against DPPH, 2,20-azinobis (3-ethylbenzothiozoline-6-sulfonic acid) radical and hydroxyl radicals with IC50 values of 395 ± 16.2 , 241 ± 11.5 and 188.6 ± 12.2 lg/ml respectively, which could be due to high amount of polyphenols and flavonoids. The observed data demonstrates 41.5 % cell survival with 100 μ M H₂O₂ challenge for 24 h, which was restored to 73 % by pre-treatment with OSE for 2h. It also decreased the lactate dehydrogenase leakage and preserved the cellular morphology. Similarly, OSE inhibited lipid peroxidation, DNA damage, ROS generation and depolarization of mitochondrial membrane. The extract restored superoxide dismutase and catalase enzyme levels and further down regulated HSP-70 over-expression. These findings suggest that OSE ameliorates H₂O₂ induced neuronal damage via its antioxidant defence mechanism and might be used to treat oxidative stress mediated neuronal disorders [169].

***Ricinus communis* L**

Ricinus communis L. (RC) belongs to family Euphorbiaceae commonly known as 'castor plant', 'palm of Christ', Endi (Hindi). It has high traditional and medicinal value for maintaining the disease free healthy life. The preliminary phytochemical study of RC revealed the presence of steroids, saponins, alkaloids, flavonoids, and glycosides [170]. This plant is extensively used in Ayurveda, Unani, Siddha, Homeopathic and Allopathic system of medicine as cathartic. Scientifically RC has been revealed to possess antioxidant activity [171], anti-fertility activity [172], hepatoprotective activity [173], anti-inflammatory activity [174], antimicrobial activity [175], antidiabetic activity [176], larvicidal activity [177], antiulcer activity [178] and many other medicinal properties. Ricin produced in the seed of castor oil plant RC, is a highly toxic, naturally occurring lectin (a carbohydrate binding protein). An experimental study by Nennesmo *et al.* showed that ricin caused an almost total loss of the dorsal root ganglionic neurons and, consequently, could prevent the formation of neuromas or eliminate an already existing neuroma. RC at lower doses, improve memory consolidation and show some neuroleptic-like properties, such as a decrease in exploratory behavior and catalepsy. The memory-improving effect and the seizure-eliciting properties were also observed with the administration of ricinine, a neutral alkaloid isolated from the RC extract. However, the neuroleptics like properties of the extract were not observed with ricinine [179]. Undecylenic acid (UDA) is an organic unsaturated fatty acid derived from castor oil. It is the

common name of 10 undecenoic acid. It has potential to ameliorate AD. UDA inhibited β -amyloid oligomerization and β -amyloid fibrillation and reversed β -amyloid-induced neuronal cell death. In addition, UDA scavenged reactive oxygen species (ROS) and reversed the levels of proapoptotic proteins induced by ROS in SH-SY5Y cells [180].

***Semecarpus anacardium* L. f**

Semecarpus anacardium L. f. (SA) belongs to family Anacardiaceae, commonly known 'Ballataka' or 'Bhilwa', is a plant well-known for its medicinal value in Ayurvedic and Siddha system of medicine, detoxified nut of SA were used in Ayurveda for skin diseases, tumors, malignant growths, fevers, haemoptysis, excessive menstruation, vaginal discharge, deficient lactation, constipation, intestinal parasites and brain tonic. It is also used for non-medicinal purpose like marking of cloth, hair dye etc. since ancient time [181]. Phytochemical analyses of SA show that, it contains a variety of biologically active compounds such as biflavonoids, phenolic compounds, bhilawanols, minerals, vitamins and amino acids [182]. Several experiments have provided anti-inflammatory activity [183], immunomodulatory activity [184], hypocholesterolemic activity [185], antioxidant activity [186], antimicrobial activity [187], anti-spermatogenic activity [188], hair growth promoter activity [189] etc. Shukla *et al.* confirmed that long-term immobilization stress produced significant neuron cell degeneration in both pyramidal (CA2) and granule cells (Dg) of hippocampal subregions. Light microscopic studies showed the presence of significant numbers of dark cell bodies in both the regions. After treatment with the extract of SA, number of degenerating cell bodies (dark cells) in pyramidal (CA2) and granule cell layer (Dg) were significantly reduced [190]. Another study conducted by Farooq *et al.* on CNS effect of nut milk extract of SA showed locomotory and nootropic activities in different experimental animal models. Loss of cholinergic cells, particularly in the basal forebrain is accompanied by the loss of neurotransmitter ACh. The SA is effective in prolonging the half-life of ACh through inhibition of AChE. SA is known to be useful in treating cognitive decline, improving memory or related CNS [191].

***Sida cordifolia* L**

Sida cordifolia L. (SC) is a perennial shrub belonging to family Malvaceae widely distributed throughout the tropical and sub-tropical plains all over India. According to Ayurveda, the plant is tonic, astringent, emollient, aphrodisiac and useful in the treatment of the respiratory system related troubles. Bark is considered as cooling. It is useful in blood, throat, urinary system related troubles, piles, etc. [192]. Phytochemical screening of SC revealed the presence of ephedrine, pseudoephedrine, quinazolines (vasicine, vasicinol), cryptoleptins, phytosterols (stearic and hexacosanoic acids, sterculic, malvalic and fumaric acid), flavonoids, saponins, asparagine, n-methyl tryptophan [193,194]. It has wide variety of therapeutic and pharmacological uses like antioxidant activity [195], analgesic activities [196], anti-inflammatory activities [197], hepatoprotective activities [198], nephroprotective effect [199], antidiabetic activities [200], antibacterial activity [201]. SC at dose level (1000mg/kg) produced sedation and significant reduction in ($p < 0.001$) spontaneous locomotion [202]. Navneet Khurana *et al.* tested aqueous and hydro-ethanolic extracts of SC (AESC and EESC respectively), in reserpine-induced orofacial dyskinesia and catalepsy along with LPO evaluated by the levels of thiobarbituric acid like reactive substances (TBARS) in rat forebrain. Repeated administration of reserpine (1 mg/kg) on alternate days (day 1, 3 and 5) for a period of 5 days significantly increased the vacuous chewing movements, tongue protrusions, orofacial bursts and catalepsy along with increased forebrain TBARS levels in rats which was dose-dependently reversed by AESC (50, 100 and 250 mg/kg; p. o.) treatment. They also predict the scope of AESC in the possible treatment of neuroleptic-induced orofacial dyskinesia and PD [203].

***Terminalia chebula* Retz**

Terminalia chebula Retz. (TC) belongs to the family Combretaceae and is one of the most important medicinal plants used in medicines of Ayurveda, Siddha, Unani and Homeopathy. It is called the "King of Medicines" in Tibet. It is commonly called as Black myrobalan,

Hilikha (Assamese). Traditionally, TC has been used to treat kidney and urinary disorders, nervous disorders, colic pain, chronic cough, sore throat, asthma, etc. It is also used as laxative, antitussive, diuretic, digestive, antidiabetic, and as a cardiotoxic remedy [204]. It is reported to contain various biochemical compounds such as triterpenes arjun glucoside 1, arjungenin and the chebulosides 1 and 2. Other constituents contains tannins, chebulic acid, chebulinic acid, tannic acid, ellagic acid, 2,4-chebulyl- β -D-glucopyranose, gallic acid, ethyl gallate, punicalagin terflavin A, terchebin, some purgative of the nature of anthraquinone, flavonoids like luteolin, rutins, and quercetin etc [205]. Scientific studies of TC reported as antioxidant [206], anticancer [207], antidiabetic [208], antimutagenic [209], antibacterial [210] and cardio-protective activities [211], anti-inflammatory activity [212]. A study by Chandrashekar R. *et al.* to evaluate the acute anxiolytic activity of aqueous extract of fruits of TC (AETC) by Light and Dark Arena in Swiss albino mice. Their results suggest that, behavioural inhibitory effects of AETC exhibited anxiolytic activity at the dose of 1.3 and 2.6 mg/kg comparable to standard drug diazepam [213]. In another study, Nageswararao *et al.* reported that acute administrations of ethanolic extracts of TC enhance the learning and memory recall ability in mice in an inverse dose-dependent manner [214]. Bhakta Prasad Gaire *et al.* investigate if fruit extract from TC might protect neuronal cells against ischemia and related diseases by reduction of oxidative damage and inflammation in rat PC12 cells using in vitro oxygen-glucose deprivation followed by reoxygenation (OGD-R) ischemia and H₂O₂ induced cell death. They found that TC extract: (1) increases the survival of cells subjected to OGD-R by 68%, and H₂O₂ by 91.4%; (2) scavenges the diphenyl-1-picrylhydrazyl (DPPH) free radical by 96% and decreases MDA levels from 237.0 \pm 15.2% to 93.7 \pm 2.2%; (3) reduces NO production and death rate of microglia cells stimulated by lipopolysaccharide. These results suggest that TC extract has the potential as a natural herbal medicine, to protect the cells from ischemic damage and the possible mechanism might be the inhibition of oxidative and inflammatory processes [215].

***Tinospora cordifolia* (Lour.) Merr**

Tinospora cordifolia (Lour.) Merr. belongs to the family Menispermaceae. The plant is commonly known as Giloe, Gurchara (Hindi), Amarlata (Assamese). A variety of active components derived from the plant like alkaloids, steroids, diterpenoid lactones, aliphatics, and glycosides have been isolated from the different parts of the plant body, including root, stem, and whole plant [216]. It's reported medicinal properties are anti-diabetic [217], anti-inflammatory [218], anti-arthritis [219], anti-oxidant [220], antistress [221], immunomodulatory [222] and anti-neoplastic activities [223]. A study by Avinash K Rawal *et al.* showed that *T. cordifolia* exhibit strong free radical scavenging properties against ROS and reactive nitrogen species as studied by electron paramagnetic resonance spectroscopy. The herb also effectively elevate the level of reduced glutathione, expression of the gamma-glutamyl-cysteine ligase and Cu-Zn superoxide dismutase genes. In addition, *T. cordifolia* significantly diminished the expression of iNOS (Inducible nitric oxide synthase) gene after 48 hours which play a major role in neuronal injury during hypoxia/ischemia [224]. Another experiment by A Shanish Antony *et al.* showed that *T. cordifolia* has potential to reduce symptom of 6-hydroxy dopamine induced Parkinsonism by protecting dopaminergic neurons and reducing the iron accumulation. Ethanolic extract of *T. cordifolia* exhibited significant increase in the dopamine levels [225].

T. cordifolia also enhances Learning and Memory. Significant response has been found in children with moderate degree of behavior disorders and mental deficit, along with improvement in IQ levels [226]. In a 21-day randomized, double-blind placebo-controlled study, the pure aqueous extract of the root was found to enhance verbal learning and logical memory [227]. *T. cordifolia* has also been shown to enhance cognition in normal rats and reverse cyclosporine-induced memory deficit. Both the alcoholic and aqueous extracts of *T. cordifolia* produced a decrease in learning scores in Hebb William maze and memory retention, indicating enhancement of learning and memory. The histopathological examination of hippocampus in cyclosporine-treated rats showed neurodegenerative changes, which were protected by *T. cordifolia* [228].

***Trapa natans* vars. *Bispinosa* (Roxb.) Makino**

Trapa natans vars. *Bispinosa* (Roxb.) Makino (TN) is commonly grown throughout India, and locally known as Water chestnut, Pani Singori (Assamese), Singhara (Hindi) in India and belongs to family Lythraceae. It has been used in the traditional system of medicine like Unani and Ayurveda since centuries for several important medicinal purposes. It has been used as nutritive, astringent, aphrodisiac, cooling, appetizer, tonic, anti-diarrhoeal etc. In Unani system of medicine, it is being used in various diseases like sexual weakness, sore throat, bilious affections, bronchitis, tuberculosis, renal calculi and fatigue etc. [229,230]. Modern researches have supported its traditional uses and also explored other important properties such as analgesic [231], immunomodulatory [232], neuroprotective [233], antioxidant activity [234], anti-microbial activity [235], antibacterial activity [236], anti-ulcer activity [237], hepatoprotective activity [238]. Analysis of chemical constituents of TN reveals the presence of flavonoids, tannins, glycosides, saponins, steroids, phenolic compound carbohydrates, proteins, vitamins and essential minerals [239-241]. Effect of hydroalcoholic extract of TN was studied on the fluorescence product and biochemical parameters like lipid peroxidation, catalase activity and glutathione peroxidase activity in brain of female albino mice. Ageing was accelerated by the treatment of 0.5 ml 5% D-galactose for 15 days. This resulted in the increased fluorescence product, increase LPO and decrease antioxidant enzyme like glutathione peroxidase and catalase in the cerebral cortex. After co-treatment with hydro alcoholic extract of TN (500 mg/kg) there was a decrease in the fluorescence product in the cerebral cortex. Moreover, TN inhibited increase LPO and restores glutathione peroxidase and catalase activity in the cerebral cortex as compared to ageing accelerated control group [242].

***Withania somnifera* (L.) Dunal**

Withania somnifera (L.) Dunal (WS) belongs to the family Solanaceae. WS, popularly known as Ashwagandha is widely considered as the Indian ginseng. In Ayurveda, it is classified as a rasayana (rejuvenation) and expected to promote physical and mental health, rejuvenate the body in debilitated conditions and increase longevity. The major biochemical constituents of Ashwagandha root are steroidal alkaloids and steroidal lactones in a class of constituents called withanolides [243]. Much of Ashwagandha's pharmacological activity has been attributed to two main withanolides, withaferin A and withanolide D. WS possesses a number of therapeutic actions which include anti-inflammatory, sedative, hypnotic, narcotic, general tonic, diuretic (Fruits & Seeds), aphrodisiac [244]. WS have antioxidant effect in the brain. WS extract can prevent increases in LPO [245]. Biochemical investigation reflected significant increase in major free-radical scavenging enzymes, superoxide dismutase, catalase and glutathione peroxidase levels in the rat brain [246]. Administered orally (50-200mg/kg orally) both sitoindosides IX and X compounds also produced significant anti-stress activity in albino mice and rats. They also augmented learning, acquisition and memory retention in both young and old rats [247]. Effects of sitoindosides VII-X and withaferin isolated from aqueous methanol extract of roots of cultivated varieties of WS were studied on brain cholinergic, glutamatergic and GABAergic receptors in male Wistar rats. The compounds slightly enhanced AChE activity in the lateral septum and globus pallidus, and decreased AChE activity in the vertical diagonal band [248]. The experimental studies have revealed that after oral administration in mice, withanoside IV is metabolized into sominone, which induces marked recovery in neuritis and synapses and also enhance axonal and dendritic out growth and synaptogenesis [249].

CONCLUSION

Herbal plants are very rich sources of phytochemicals and other active constituents which are responsible for increasing nootropic activity. The rising cases of neurodegenerative disorders and poor understanding of its mechanism of development and pathogenesis hinders researchers in developing proper cure for patients afflicted with them. In traditional practice of medicines, various plants have been used for neuroprotection. This manuscript has provided an ethnopharmacological approach which leads to identifying potential

plant sources to ameliorate different neurodegenerative disorders. It is apparent from the manuscript that a variety of plants from NE India show potential for the treatments of neurological disorders. However, further experimental studies regarding the compounds responsible for the exact mechanism and isolation of active ingredients involved are necessary.

CONFLICT OF INTERESTS

Declared None

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