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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, Neurototoxicity, 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 neurototoxicity
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 i onotropic 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 Ca2+ 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. Neurprotective 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*

*Acorus calamus* L. (AC) which is also known as Sweet flag (English), Bach (Assamence) 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 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 evinoinate, sesquiterpene, alkaloids panaxanin A, panaxatine B and wiformine F, celastrine, celapanine, celapagine, polyalcohol (malangunin, malkanginnol, malkanguniol and malkanguniol β), triterpenoids (pristimerin, amyristic acid, 3β,24α,25-trihydroxylanost-24-en-3β-ol, 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 (NMDA). 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 avoidance in both the shuttle-box and step-through latency in the 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].

**Bacopa monnieri**

*Bacopa monnieri* (L.) wettest. 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.) Wetstt. (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, Pokat (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 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]. Asiatric acids isolated from CA showed enhanced learning and memory properties in male Snaque–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 butyrilcholinesterase (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], antispasmodic [48], anticonvulsant [49], sedative [50], immunomodulant [51], cardiodepressive [52], anti diabetic [53], cytotoxic and antitumor [54], antiviral [55], bacteriostatic [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], anti fungal 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 Bishit 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 in rat brains and decreases cerebral inflammatory indices, LPO and calcium levels in ex perimental rat. It also attenuated reactive changes in brain histology like gliosis, lymphocytic infiltration and cellular edema [81]. Another study by Vasedevan 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 stigmas 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 acidal, aphrodisiac, analgesic, anti-inflammatory, antispasmodic, bitter, cephalalgia, 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 anti hypertensive, anticonvulsant, antirheumatic, anti genotoxic, antitumor, cyto toxic, antispasmodic, bitter, 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 and crocin on L-dopa induced parkinsonism. 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 dimethyl crocetin [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, 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 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 turmerone, allantone, and zingerberene. 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 curumin, demethoxycurcumin, bisedmethoxycurcumin and calebin-A and some of its synthetic analogues, were shown to protect PC12 cells
from β-amylol 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 μg/mg/ml) prior to hydrogen peroxide (H₂O₂) exposure significantly prolonged cell survival, increased antioxidant enzyme activity and decreased MDA concentration. This anti-oxidant activity, thus, supports 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.)**

_Eclipta prostrata_ (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 Ayurvedic 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], anti-cancer 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. Phyto chemical 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], antiinflammatory [120], hepatoprotective [121], anti-infective [122], anti-diarrheal [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, anti convulant and anti-stress activity [126].

**Glycyrrhiza glabra L.**

_Glycyrrhiza glabra_ L. (GG) belongs to family Leguminoseae. GG is commonly known as Yashhtimadhu, licorice. It is reported to have antiviral [127], anticancer [128], anti-ulcer [129], anti-diabetic, anti-oxidant [130], immunomodulatory activity [131], antimicrobial activity [132], anti-inflammatory activity [133], anticonvulant [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 increased 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 (NVT) results indicate that only improved learning and memory of mice. Yashtimadhu significantly protected neurons from neurotoxins in in vitro and in vivo models [155]. AD is another
were not observed with ricinine [179]. Undecylenic acid (UDA) is an administration of ricinine, a neutral alkaloid isolated from the RC extract. However, the neuroleptic-like properties of the extract of the seed of castor oil plant RC, is a highly toxic, naturally occurring lectin. 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-inflammatorv activity [174], antimicrobial activity [175], anti-diabetic activity [176], larvicidal activity [177], anti-ulcer activity [178], 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 disorders. 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 anxiolytic and antidepressant properties at the same dose and can be a potential therapeutic agent against mixed anxiety and depressive syndrome. A study by Mahmood Samini 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, 2,2-azinobis (3-ethylbenzothiazoline-6-sulphonic acid) radical and hydroxyl radicals with IC50 values of 395 ± 16, 241 ± 11.5 and 108.6 ± 12.2 μg/ml respectively, which could be due to high amount of polyphenols and tannins. The observed data confirmed that long term immobilization 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 oxidative stress mediated neuronal disorders [169].

**Ocimum sanctum**

**Ocimum sanctum** (OS) or '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]. The presence of ephedrine, pseudoephedrine, quinazolines (vasicine, vasicinol), cryptoponins, phytostersols (stearic and hexacosanoic acids, sterolic, malvolic 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], anti-diabetic activities [200], antibacterial activity [201]. SC at dose level (1000mg/kg) produced sedation and significant reduction in light dark test, elevated plus maze test, and hole-board test. The OS extracts show anxiolytic and antidepressant properties at the same dose and can be a potential therapeutic agent against mixed anxiety and depressive syndrome. A study by Mahmood Samini et al. showed neuroprotective activity of OS in rotenone induced PD in Rats [168]. 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 oxidative stress mediated neuronal disorders [169].

**Ricinus communis**

**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], anti-diabetic activity [176], larvicidal activity [177], anti-ulcer 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 neumors or eliminate an already existing neurona. RC at lower doses, improve memory consolidation and show some neuroprotective-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 neurotoxicity properties of the extract were not observed with ricine [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].

**Semenacarpus anacardium L.**

Semenacarpus anacardium L. f. (SA) belongs to family Anacardiaceae, commonly known 'Ballataka' or 'Bilwaa', 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, fever, 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, bilavanol, 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-spermatoenic activity [188], hair growth promoter activity [189] etc. Shukla et al. confirmed that long term immobilization 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 oxidative stress mediated neuronal disorders [169].

**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, astrigent, 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), cryptoponins, phytostersols (stearic and hexacosanoic acids, sterolic, malvolic 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], anti-diabetic activities [200], antibacterial activity [201]. SC at dose level (1000mg/kg) produced sedation and significant reduction in light dark test, elevated plus maze test, and hole-board test. The OS extracts show anxiolytic and antidepressant properties at the same dose and can be a potential therapeutic agent against mixed anxiety and depressive syndrome. A study by Mahmood Samini et al. showed neuroprotective activity of OS in rotenone induced PD in Rats [168]. 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 oxidative stress mediated neuronal disorders [169].

**Terminalia chebula Retz.** (TC) belongs to the family Combretaceae and one of the most important medicinal plants used in medicines of Ayurveda, Siddha, Unani, and Homoeopathey. It is also called the "King of Medicines" in Tibet. It is commonly called as Black myrobalan,
Hilika (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 cardiotonic remedy [204]. It is reported to contain various bioactive compounds such as terpenoids, alkaloids, steroids, saponins, tannins, and flavonoids [205]. TC has been observed to exhibit strong free radical scavenging properties against reactive oxygen species and also has anti-inflammatory activity [212]. A study by Chandrashekar R. et al. revealed that the pure aqueous extract of the root was found to enhance verbal learning and logical memory [227]. Controlled study, the pure aqueous extract of the root was found to exhibit anxiolytic activity in mice in an inverse dose-dependent manner [214]. Bhakta Prasad G. et al. investigated whether 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-pyrrylhydrazyl (DPPH) free radical by 96% and decreases MDA levels from 237.0 ± 15.2% to 93.7 ± 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, Gurcha (Hindi), Amarilata (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-arthritic [219], anti-oxidant [220], anti-tussive [221], immunomodulatory [222] and anti-neoplastic activities [223]. S. C. et al. by Avinash Davel 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-cysteinyl 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. Ethanol 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 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 China. After co-treatment with hydroalcoholic 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 aged 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 withanolid 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 VH-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 outgrowth 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 mechanisms of development and pathogenesis hinder 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.

CONFICT OF INTERESTS
Declared None

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