

Phytochemicals Having Neuroprotective Properties from Dietary Sources and Medicinal Herbs

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ABSTRACT

Many neuropsychiatric and neurodegenerative disorders, such as Alzheimer's disease, anxiety, cerebrovascular impairment, depression, seizures, Parkinson's disease, etc. are predominantly appearing in the current era due to the stress full lifestyle. Treatment of these disorders with prolonged administration of synthetic drugs will lead to severe side effects. In the recent years, scientists have focused the attention of research towards phytochemicals to cure neurological disorders. Nootropic herb refers to the medicinal role of various plants/parts for their neuroprotective properties by the active phytochemicals including alkaloids, steroids, terpenoids, saponins, phenolics, flavonoids, etc. Phytochemicals from medicinal plants play a major part in maintaining the brain's chemical balance by acting upon the function of receptors for the major inhibitory neurotransmitters. Medicinal plants viz. *Valeriana officinalis*, *Nardostachys jatamansi*, *Withania somnifera*, *Bacopa monniera*, *Ginkgo biloba* and *Panax ginseng* have been used widely in a variety of traditional systems of therapy because of their adaptogenic, psychotropic and neuroprotective properties. This review highlights the importance of phytochemicals on neuroprotective function and other related disorders, in particular their mechanism of action and therapeutic potential.

Key words: Neuroprotection, Phytochemicals, Medicinal herbs, Nootropics, Dietary sources.

INTRODUCTION

Neuroprotection refers to the strategies and relative mechanisms able to struggle down the Central Nervous System (CNS) against neuronal damage caused by various neuropsychiatric and neurodegenerative disorders such as Alzheimer's disease, anxiety, cerebrovascular impairment, seizures, Parkinson's disease, etc. Neurodegenerative diseases are estimated to be the second most common cause of death among elderly by the 2040s.¹ Among the strategies for neuroprotection, phytochemicals may represent a valuable remedy in preventing neurodegenerative diseases. Many categories of natural and synthetic neuroprotective agents have been reported, however, synthetic neuroprotective agents are believed to have

certain side effects such as dry mouth, tiredness, drowsiness, sleepiness, anxiety or nervousness, difficulty with balance, etc. Herb based medicated products have drawn considerable awareness from research bases and industries in recent years at the national and international levels.² Hence, there has been intense interest focussed on the part of potential phytochemicals to modulate neuronal function and protective mechanism against neurodegeneration. As complementary and alternative therapy, herbal medicine or phytotherapy, refers to the medical utilization of plant components (leaves, stems, roots, flowers, fruits and seeds) for their curative properties. Generally, herbal products contain a variety of bioactive phytochemicals, including alkaloids, steroids, terpenoids, saponins, phenolics, flavonoids, etc. and it is difficult to specify which part of the herb has biologically active for special discourse. The researchers around the globe are searching for bioactive phytochemicals from the herbs which are being used as neuroprotective in traditional medicine like Chinese medicinal system, Indian Ayurvedic medicine system, Korean system of medicine, Mediterranean system of medicine, etc. This review will highlight the medicinal herbs from different traditional systems, their bioactive phytochemicals on neuroprotective function and other related disorders, in particular their mechanism of action

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and therapeutic potential.

Neurodegenerative diseases

Neurodegenerative diseases are progressive disorders of central nervous system that affect on the central and peripheral nervous systems. Gradual and progressive loss of neural cells may lead to neurodegeneration. Many factors are known to play a direct role in the initiation of neurodegeneration, free radical formation by the Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) is the main causative factor. Neuroinflammatory process is known to play a crucial role in the progress of several neurodegenerative diseases. According to the reports of the National Institute of Neurological Disorders and Stroke, there were more than 600 neurological disorders recorded worldwide.³ Some of them were briefly discussed in this review at length.

Anxiety

Anxiety is characterised by psychological and physiological state in which cognitive, somatic, emotional, and behavioral components are involved. It can increase to an extent that may interfere with even normal routine of life and person may feel apprehensive regarding happenings of normal things in life. Anxiety disorders comprise seven clinical conditions⁴ such as (a) Generalized Anxiety Disorder (GAD): In this condition person will have persistent fear and worry and become overly concerned with everyday matters. (b) Panic disorder: Person suffers from brief attacks of intense terror and apprehension, often marked by confusion, dizziness, trembling, shaking, nausea, difficulty breathing. (c) Phobias: In which fear and anxiety is triggered by a specific stimulus or situation. Agoraphobia: It is specific anxiety about being in a place or situation where escape is difficult or embarrassing or where help may be unavailable. (d) Social Anxiety Disorder (SAD): It is an intense fear of negative public scrutiny or of public embarrassment or humiliation. (e) Obsessive-Compulsive Disorder (OCD): It is primarily characterized by repetitive obsessions and compulsions. (f) Post-Traumatic Stress Disorder (PTSD): It is resulted from an extreme situation, such as major accident, child abuse, war situation, natural disaster, rape, hostage situations, etc. (g) Separation anxiety disorder: It is the feeling of inappropriate or excessive levels of anxiety over being separated from a place or person. Monoamines (dopamine, noradrenaline and serotonin), neuropeptides (galanin, neuropeptide Y, arginine vasopressin, tackykinin), neurosteroids and cytokines have been observed to play a modulators role in anxiety states.

Attention Deficit/ Hyperactivity Disorder

Attention Deficit/Hyperactivity Disorder (ADHD) is a loosely defined assemblage of neuropsychiatric symptom clusters that emerge in childhood and often persist into adulthood. ADHD is observed with increasingly employed as a diagnostic label for individuals who display a wide range of symptoms, such as inability to stay focused, restlessness, mood swings, temperament, problems in completing tasks, disorganization and inability to cope with stress.⁵

Depression

The term depression indicates a dampened mood and pervasive unhappiness. Depression is one of the most common emotional disorders, it may be manifested in varying degrees from feelings of slight sadness to utter misery and dejection. Changes in mood and the occurrence of depressive symptoms are determined by the biological as well as an environmental factor. According to World Health Organization (WHO), approximately 450 million people are suffering from a mental or behavioral disorder, and is predicted to increase significantly by 2020. Depression is one of the top ten causes of morbidity and mortality worldwide based on a survey by the WHO. In depressed conditions, there are several structural alterations of neurons that will take place such as, a decreased volume of the frontal cortex and hippocampus, dysfunctions of HPA axis, abnormalities in 5-HT and its receptors.⁶ It is well established that the 5-HT is a monoaminergic neurotransmitter which is also dysregulated in other neurological disorder conditions such as, anxiety and schizophrenia.⁶

Dementia

Parkinson's Disease (PD) is a serious motor disorder and the most common brain degenerative disease in humans.⁷ The loss of dopaminergic neurons in the substantia nigra is the most pervasive factor to contribute the characteristic symptoms of PD. It is characterized by four main symptoms: tremor, rigidity, bradykinesia and impairment of balance. The classic pathological findings are the presence of Lewy bodies in the substantia nigra, and loss of nerve cells in portions of its ventral tier.⁷ Besides the neuropathologic symptoms, PD can be caused neurochemically by a consistent deficit in cholinergic neurotransmission. Alzheimer's Disease (AD) is a neurodegenerative disorder, which is characterized by deficit, learning and memory loss followed by cognitive disorders like depression, agitation and psychosis.

Epilepsy

Epilepsy is the most common neurological disorder, which affects almost 50 million worldwide.⁸ It is characterized by unpredictable occurrence of periodic epileptic seizures, i.e. involuntary contraction of striated muscle repeatedly. Seizures take place due to excessive and rapid discharge of cerebral neurons in the gray matter of the brain. In epilepsy, impaired voltage-sensitive sodium and calcium-channel functioning impaired GABA-mediated inhibition and excessive glutamate-mediated neurotransmission may trigger a cascade of events leading to neuronal damage and cell death.

Excitotoxicity

Excitotoxicity plays a key role in intoxication of some poisons like domoic acid (Amnesic shellfish poison by marine algae), kainic acid, etc. Excitotoxicity is the pathological process by which nerve cells are damaged and killed by excessive glutamate stimulation. Excitotoxicity may also express in different pathological conditions like, spinal cord injury, traumatic brain injury, multiple sclerosis, stroke, amyotrophic lateral sclerosis, and other neuronal disorders.⁹ It is also involved in most aspects of normal brain functions including cognition, memory, and learning. Excitotoxicity can occur through over-activation of the NMDA receptor with the subsequent influx of Ca^{2+} , activation of both nitric oxide and iNOS, and excess generation of $\text{NO}\cdot$.¹⁰

Schizophrenia

It is one of the most important forms of psychiatric illness. In this condition patient don't know what is happening at present. The symptoms of this disease are 2 types: 1) positive symptoms: delusions, hallucination, thought disorders, abnormal behavior. 2) Negative symptoms: withdrawal from social contact, flattening of emotional responses. The level of neurotransmitters such as dopamine, 5-HT, acetylcholine and norepinephrine levels upregulate in the brain in this condition.¹¹

Neuroregeneration

Neuroregeneration is a concept which encompasses endogenous neuroprotection leading to neuroplasticity and neurite outgrowth.¹² It has been suggested that restoration of the neuronal and synaptic networks in the injured brain is necessary for the recovery of brain functions. It was once believed that nerve regeneration in the mammalian Central Nervous System (CNS) was irreversible, but recently it has

become apparent that damaged neurons do regenerate in an active process under the presence of stimulatory substances such as Nerve Growth Factor (NGF) and Brain Derived Neurotrophic Factor (BDNF).¹³ The role of neuroprotection involves a number of effects including a potential role against injury induced by neurotoxic species, an ability to suppress neuro-inflammation and to promote effective cognitive function. Recent studies suggest that different traditional neuroprotective herbal extracts/ isolated phytochemicals have potential role in prevention of neurodegeneration. Evidence also exists for the neuromodulatory effects of phytochemicals and suggests that these phytochemicals may induce beneficial effects on the vascular system leads to change in cerebrovascular blood flow and modulation of neuronal function. Hence natural products may harmonize very well for the treatment of neuronal injury.¹⁴ Lately, many compounds from natural sources have been demonstrated to possess neurotrophic and neuroprotective abilities.

Phytochemical based antioxidants in neuroregeneration

Phytochemical based antioxidants may have neuroprotective and neuroregenerative roles by reducing or reversing cellular damage and by slowing progression of neuronal cell loss.¹⁵ In nature, antioxidants are grouped as endogenous or exogenous, the endogenous group includes enzymes like Superoxide Dismutase (SOD), Catalase (CAT), Glutathione peroxidase (GPx), and several proteins like albumin, ceruloplasmin, Haptoglobin and transferrin. The most important exogenous antioxidants are dietary phytochemicals (polyphenols, phenolic acids, flavonoids, terpenoids, saponins etc.) and vitamins (ascorbic acid, alpha-tocopherol, and beta-carotene).¹⁶ Antioxidants offer a promising approach in the control or slowing down progression of several neurodegenerative disorders leading to changes in cerebrovascular blood flow such as, Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, ischaemic stroke, haemorrhagic stroke and Parkinson's disease.¹⁶ In normal condition, a steady-state exists between pro-oxidants and antioxidants. However, when the rate of free radical generation exceeds the capacity of antioxidant defenses, oxidative stress promotes consequential severe damage to cellular machinery. Oxidative stress is associated with dysfunction in mitochondrial and endoplasmic reticulum, which includes apoptosis and protein misfolding in neurons. During neurodegenerative state, there would be decreased activities of antioxidant enzymes such as SOD, CAT, GPx, and GSH, which signify the role of antioxidants in neuroprotection.

An increase in Reactive Oxygen Species (ROS) and Reactive

Nitrogen Species (RNS) have also been proposed to play major role in many neurodegenerative disorders.¹⁷ Redox regulation of neuronal survival at the level of transcription, which includes transcription factor alternations such as nuclear factor- κ B (NF- κ B), activating protein-1 (AP-1), nuclear factor erythroid 2 (Nrf2), and Hypoxia Inducible Factor (HIF) may affect overall oxidative status.¹⁸ Furthermore, redox regulation of neuronal survival at the signal-transduction level influences the mitogen-activated protein kinase and PI3K/Akt pathways, as well as several redox sensitive apoptotic effectors such as caspases, Bcl-2, and cytochrome C, and their functions can be significantly affected by cellular ROS. There is an abundant evidence that flavonoids are effective in blocking oxidant induced neuronal damage by preventing the activation of caspase-3. The flavanols, epicatechin and 3'-O-methyl- epicatechin protect neurons against oxidative damage by suppressing JNK, C-gun and pro-caspase-3.¹⁹ The flavanones, hesperetin, 5-Nitro-hesperetin have observed to inhibit oxidant-induced neuronal apoptosis by activation of important protein and lipid kinase signalling pathways.¹⁹

Traditional herbs for neuroprotection

Nootropic is a term used for the medical drugs or nutritional supplements that have a positive effect on brain function.²⁰ A number of pharmaceutical compounds are in the market, which have been used for their neuroprotective property by altering the balance of particular brain functioning chemicals (neurotransmitters). Some of the drugs act on the enhancement of cerebral blood flow, metabolic rate of cerebral oxygen usage and metabolic rate of cerebral glucose in chronic impaired human brain function, i.e., stroke, poor brain blood flow, dementia and pseudo dementia. Several medicines are derived from the medicinal herbs and have shown memory enhancing properties by virtue of their proactive phytochemical constituents. One of the mechanisms suggested to dementia is decreased cholinergic activity in the brain. Therefore, cholinergic drugs (of plant origin) like: Muscarinic agonists (e.g. Arecoline, Pilocarpine etc.), nicotinic agonists (e.g. Nicotine) and cholinesterase inhibitors (e.g. Huperzine) can be employed for improving memory.²⁰ Some other classes of drugs used in dementia are: Stimulants or Nootropics (e.g. Piracetam, amphetamine), putative cerebral vasodilators (e.g. Ergot alkaloids, papavarine) and calcium channel blocker (e.g. Nimodipine).

In the present era, a sudden increase in neurological disorders and recognition of severe side effects associated with long term administration of synthetic drugs has alarmed the attention of researchers towards natural

resources. Medicinal plants like *Bacopa monniera*, *Ginkgo biloba*, *Panax ginseng*, *Nardostachys jatamansi*, *Valeriana officinalis* and *Withania somnifera* have been used extensively in various traditional systems of therapy because of their adaptogenic, psychotropic and neuroprotective properties. *Ginkgo biloba* has been prescribed in the Europe over the past two decades for the treatment of cerebral insufficiency, which is roughly equivalent to vascular dementia, includes memory loss, absent minds, confusion, depression, anxiety, dizziness and headache.²¹ Recently, several traditional Chinese medicines and Indian herbal medicines (Ayurveda) have been reported to be neuroprotective via regeneration of the neuronal network. There are more than 120 traditional medicines that are being used for the therapy of CNS disorders in Asian countries.²² In the Indian system of medicine the following medicinal plants have shown promising activity in neuropsychopharmacology: *Acorus calmus*, *Allium sativum*, *Angelica sinensis*, *Bacopa monniera*, *Centella asiatica*, *Celastrus paniculatus*, *Crocus sativus*, *Curcuma longa*, *Enhydra fluctuans*, *Ginkgo biloba*, *Glycyrrhiza glabra*, *Huperiza serrata*, *Hypericum perforatum*, *Nicotiana tabacum*, *Phyostigma venosum*, *Salvia officinalis*, *Terminalia chebula*, *Uncaria tomentosa*, *Valeriana wallichii*, *Withania somnifera* etc. Some of herbs being used in Chinese medicine are: *Angelica pubescens*, *Ledebouriella divaricata*, *Ligusticum chuanxiong*, *Morus alba*, *Salvia miltiorrhiza*, *Scutellaria baicalensis* and *Uncaria rhynchophylla*. Table-I describes an overview of some of the medicinal herbs with nootropic properties and their mechanism of action.

Biochemical action of some of the neuroprotective herbs

Bacopa monniera

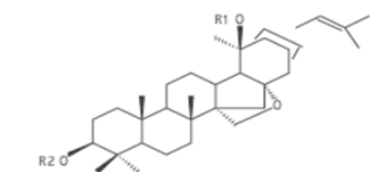
“*Brahmi*,” has been used in the Ayurvedic system of medicine for centuries as a brain tonic for learning, memory enhancement and anti stress agent in anxiety.²³ it contains many bio active phytochemicals like herpestine (alkaloids), d-mannitol, hersaponin and monnierin (saponins). Major active constituents have been identified as numerous bacosides and bacopasaponins (Figure.I-I). The constituents responsible for *Bacopa*'s cognitive effects are bacosides A and B.²⁴ The bacosides aid in repair of damaged neurons by enhancing neuronal synthesis, kinase activity, restoration of synaptic activity, and nerve impulse transmission.

Centella asiatica

Centella asiatica is belonging to the family Apiaceae (*Umbelliferae*) is a psychoactive medicinal plant being used

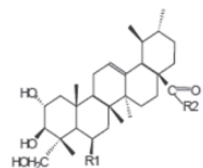
Table 1: Medicinal herbs, their active constituents and mechanism of action				
Scientific name	Phytochemical group	Active constituents	Possible mechanism of action	References
Anxiolytic herbs				
<i>Cassia siamea</i> (Caesalpinaceae)	Phenolics	Barakol	Dopamine agonistic and 5-HT ₂ antagonist like effects	Sukma et al ⁶⁸
<i>Magnolia officinalis</i> (Magnoliaceae)	Polyphenols	Honokiol, Magnolol, Honokiol	Modulation of GABAA and GABAC receptors	Ai et al ⁶⁹
<i>Passiflora incarnate</i> (Passifloraceae)	Flavonoids	Chrysin	Enhancing GABAA/BDZ receptors	Dhawan et al ⁷⁰
<i>Piper methysticum</i> (Piperaceae)	Kavalactones	Methysticin, Kavain, Yangonin	Modulation of GABAA receptors	Feltenstein et al ⁷¹
<i>Scutellaria baicalensis</i> (Labiatae)	Flavonoids	Wogonin, Baicalein, Baicalin	Modulation of GABAA/BDZ receptor complex	Liao et al ⁷²
<i>Tilia tomentsa</i> (Tiliaceae)	Flavonoids	Chrysin, Kaempferol	Modulation of BDZ receptor complex	Viola et al ⁷³
<i>Withania Somnifera</i> (Solanaceae)	Glyco withanolides	Sitoindoside IX and Sitoindoside X	Antioxidant action	Bhattacharya et al ⁷⁴
<i>Ziziphus jujube</i> (Rhamnaceae)	Saponins	Spinosin, Jujubosides	Inhibition of hippocampal hyperactivity	Shou et al ⁷⁵
Antidepressant herbs				
<i>Apocynum venetum</i> (Apocynaceae)	Flavonoids	-	Medicating central monoaminergic systems	Kim et al ⁷⁶
<i>Areca catechu</i> (Arecaceae)	Alkaloids	Arecaidine, Arecoline, Guvacine	Inhibition of MAO-A	Dar and Khatoun ⁷⁷
<i>Bacopa monniera</i> (Scrophulariaceae)	Saponins	Bacoside A	Antioxidant action	Singh and Dhawan ²⁴
<i>Cissampelos sympodialis</i> (Menispermaceae)	-	Warifteine	Antioxidant action	Thomas et al ⁷⁸
<i>Curcuma longa</i> (Liliaceae)	Flavonoid	Curcumin	Inhibition of MAO-A	Park and Kim ⁷⁹
<i>Hypericum perforatum</i> (Hypericaceae)	Flavonoids	Hyperforin, Rutin	Inhibition of 5-HT, DA, MAO-A, MAO-B and NE reuptake	Cervo et al ⁸⁰
<i>Morinda officinalis</i> (Rubiaceae)	Oligosaccharides	-	Antioxidant action	Cui et al ⁸¹
<i>Perilla frutescens</i> (Lamiaceae)	Poly phenols	Rosmarinic acid, Caffeic acid, Apigenin		Takeda et al ⁸²
<i>Withania somnifera</i> (Solanaceae)	Alkaloids	Withanolides and withanols	Mood stabilizing action	Bhattacharya et al ⁷⁴
Anti dementia herbs				
<i>Angelica sinensis</i> (Apiaceae)	Poly phenol	Ferulic acid	Antioxidant action	Yan et al ⁸³
<i>Biota orientalis</i> (Cupressaceae)	Diterpenes	Pinusolides	Neuroprotection	Koo et al ⁸⁴
<i>Centella asiatica</i> (Apiaceae)	Saponins	Asiaticoside, oxyasiaticoside, centelloside, brahmoside, brahminoside	Antioxidant action; AChE inhibitor activity	Veerendra Kumar and Gupta ⁸⁵
<i>Dipsacus asper</i> (Dipsacaceae)	Saponins	-	Antioxidant action	Qian et al ⁸⁶
<i>Galanthus nivalis</i> (Amaryllidaceae)	Alkaloid	Galanthamine	A potent AChE inhibitor, enhances cholinergic nicotinic neurotransmission	Woodruff-Pak et al ⁸⁷
<i>Gastrodia elata</i> (Orchidaceae)		Gastrodin, Vanillin	Inhibition of GABA transaminase	An et al ⁸⁸
<i>Ginkgo biloba</i> (Ginkgoaceae)	Terpenoids	bilobolide, ginkgolides,	Inhibition of h-adrenoreceptors, antiagonistic effects on GABAA receptors	Hoyer et al ⁸⁹
<i>Huperzia serrata</i> (Huperziaceae)	Sesquiterpene alkaloid	Huperzine A	Potent AChE inhibitor	Wang et al ⁹⁰
<i>Hypericum perforatum</i> (Hypericaceae)	Flavonoids	Hyperforin	Facilitating adrenergic and 5-HT _{1A} receptors	Klusa et al ⁹¹
<i>Paeonia lactiflora</i> (Paeoniaceae)		Paeoniflorin	Modulating adrenergic systems	Ohta et al ⁹²
<i>Panax ginseng</i> (Araliaceae)	Triterpene saponins	Ginsenosides, Panaxynol	Inhibiting h-AP, enhancing Ach and neurotrophic activity	Hsieh et al ⁹³
<i>Salvia miltiorrhiza</i> (Lamiaceae)	-	Lithospermate B	Mediation of central DA, NE, and 5-HT Systems	Cheng et al ⁶⁶
<i>Schizandrae chinensis</i> (Magnoliaceae)		Schizandrin	Acting at ACh, 5-HT ₂ , 5-HT _{1A} and GABAA receptors	Zhang ⁹⁴
Uncaria				

<i>Tomentosa</i> (Rubiaceae) <i>Uncaria</i>	Alkaloids	Uncarine E, Rhynchophylline	Positive modulation of M1, 5-HT2 and NMDA receptors AChE inhibitory activity	Kang <i>et al</i> ⁹⁵ Yan <i>et al</i> ⁸³
<i>Angelica archangelica</i> (Umbelliferae) <i>Areca catechu</i>	Methanol extract Alkaloids	Arecoline, talsaclidine	Muscarinic (M2) binding activity	Houghton and Seth ⁹⁶
<i>Celastrus paniculatus</i> (Celastraceae)	Seed oil		Inhibits the levels of noradrenaline, dopamine and 5-hydroxy tryptamine (5-HT)	Gattu <i>et al</i> ⁹⁷
<i>Curcuma longa</i> (Liliaceae)	Flavonoid	Curcumin	Reverse chronic stress-induced impairment of hippocampal neurogenesis and increase expression of brain-derived neurotrophic factor	Xu <i>et al</i> ⁴⁷
<i>Huperzia serrata</i> (Huperziaceae)	sesquiterpene alkaloid	Huperzine A	Neuroprotective against β -amyloid peptide fragment	Wang <i>et al</i> ⁹⁰
<i>Magnolia officinalis</i> <i>Melissa officinalis</i>	Biphenolic lignans Flavonoids	Honokiol, magnolol	Inhibiting ROS formation Acetylcholine receptor activity in the central nervous system with both nicotinic and muscarinic binding properties	Ai <i>et al</i> ⁶⁹ Perry <i>et al</i> ⁹⁸
<i>Nardostachys jatamansi</i> (Valerianaceae)	Sesquiterpenes lignans and neolignans,	Jatamansic acid, Jatamansone, Nardostachysin	Dopamine enhancing property	Rao <i>et al</i> ⁹⁹
<i>Salvia lavandulaefolia</i>	Cyclic monoterpenes	1,8-cineole, α -pinene, β -pinene	AChE inhibitory activity	Perry <i>et al</i> ⁹⁸
Anticonvulsing herbs				
<i>Aconitum</i> sp., (Ranunculaceae)	Alkaloids	Aconitine, Lappaconitine, Heteratisine, Mesaconitine	Activate NMDA receptor mediated responses and involvement of alpha receptor	Ameri <i>et al</i> ¹⁰⁰
<i>Angelica dahurica</i> (Apiaceae) <i>Berberis vulgaris</i> (Berberidaceae)	Furanocoumarin Isoquinoline alkaloid	Phellopterin Berberine	BZD receptors agonist Modulates neurotransmitter systems like NMDA, nitric oxide and serotonin	Bergendorff <i>et al</i> ¹⁰¹ Bhutada <i>et al</i> ¹⁰²
<i>Crocus sativus</i> (Liliaceae)		Safranal	GABA(A)-BZD receptor complex	Hosseinzadeh and Khosravan ¹⁰³
<i>Cymbopogon citratus</i> (Gramineae) <i>Cynanchum otophyllum</i> (Apocynaceae)	Essential oil Otophyllside	Alkaloids	GABA ergic neurotransmission Inhibition of tubulin synthesis and reduction in mossy fibre sprouting and neosynaptogenesis	Blanco <i>et al</i> ¹⁰⁴ Mu <i>et al</i> ¹⁰⁵
<i>Ficus platyphylla</i> (Moraceae)	Saponin		Suppresses excitatory and inhibitory synaptic traffic; blocks sustained repetitive firing and spontaneous action potential firing; impairs membrane excitability	Chindo <i>et al</i> ¹⁰⁶
<i>Fraxinus griffithii</i> (Oleaceae)		Ligustrosid	Increases GABA- facilitated inhibition in CNS through interaction with GABA-BZD-BARB/PICRO-CL receptor complex	Basori ¹⁰⁷
<i>Ginkgo biloba</i> (Ginkgoaceae)	Sesquiterpene	Bilobalide	Elevation in hippocampal GABA levels through potentiation of glutamic acid decarboxylase activity;	Rodriguez ¹⁰⁸
<i>Nigella sativa</i> (Ranunculaceae)	Anthraquinone	Thymoquinone	Opioid receptor mediated increase in GABAergic tone	Hosseinzadeh and Parvardeh ¹⁰⁹
<i>Ocimum sanctum</i> (Lamiaceae)	Essential oil		Involvement of dopaminergic neurons	
<i>Panax ginseng</i> (Araliaceae)	Triterpenes	Ginsenosides	Increases glutamate decarboxylase enzyme activity which increase the GABA level in brain	Choi <i>et al</i> ¹¹⁰
<i>Piper nigrum</i> (Piperaceae)	Alkaloids	Piperine	Antagonist action at NMDA receptors	D'Hooge <i>et al</i> ¹¹¹
<i>Rubia cordifolia</i> (Rubiaceae)	Terpenoids		Raises GABA and 5- HT contents in brain	Kasture <i>et al</i> ¹¹²



	R ₁	R ₂
Bacoside A	H	α-L-arabinofuranosyl (1-3) α-L-arabinopyranosyl
Bacoside B	H	β-D-glucopyranosyl (1-3)-O- α-L-arabinofuranosyl 1-2
Bacosaponin B	H	α-L-arabinofuranosyl (1-2) α-L-arabinopyranosyl

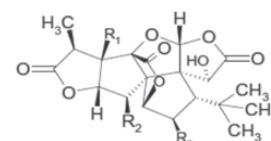
i) Bacosides (*Bacopa monniera*)



ASIATICOSIDE

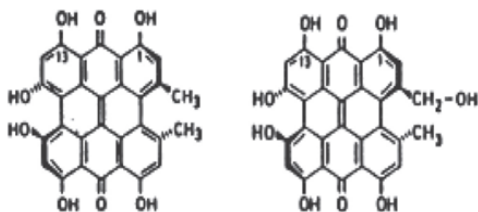
	R ₁	R ₂
1. Asiatic acid	-H	-OH
2. Madecassic acid	-OH	-OH
3. Asiaticoside	-H	-O-gluc-gluc-Rha
4. Madecassoside	-OH	-O-gluc-gluc-Rha

ii) Asiaticosides (*Centella asiatica*)



Ginkgolide A:	R ₁ =OH, R ₂ =H, R ₃ =H
Ginkgolide B:	R ₁ =OH, R ₂ =OH, R ₃ =H
Ginkgolide C:	R ₁ =OH, R ₂ =OH, R ₃ =OH
Ginkgolide J:	R ₁ =OH, R ₂ =H, R ₃ =OH
Ginkgolide M:	R ₁ =H, R ₂ =OH, R ₃ =OH

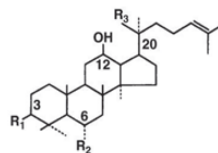
iii) Ginkgolides (*Ginkgo biloba*)



Hypericin

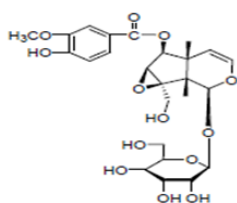
Pseudohypericin

vi) Naphthodianthrones (*Hypericum perforatum*)

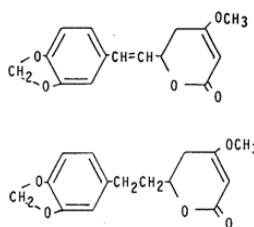


Ginsenosides	R ₁	R ₂	R ₃
Ginsenoside-Rg1	-OH	-O-Glc	-O-Glc
Ginsenoside-Rb1	-O-Glc2-Glc	-H	-O-Glc6-Glc

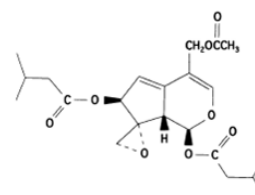
v) Ginsenosides (*Panax ginseng*)



vi) Picroside II (*Picrorhiza scrophulariflora*)

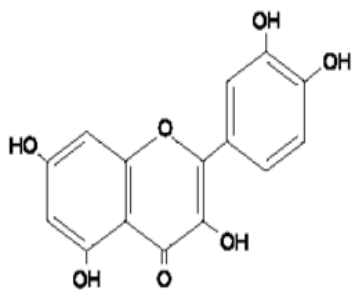


vii) Methysticin and dihydromethysticin (*Piper methysticum*)

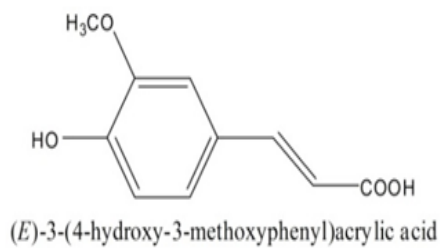


viii) Valepotriates (*Valeriana wallichii*)

Figure 1: Structures of bioactive compounds of certain nootropic herbs

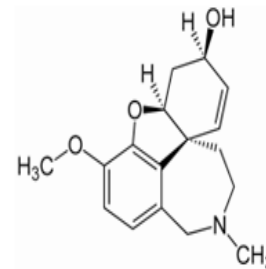


xviii) Quercetin

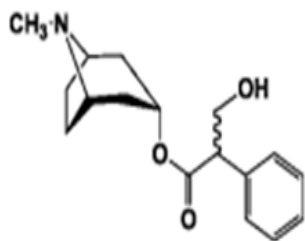


(*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylic acid

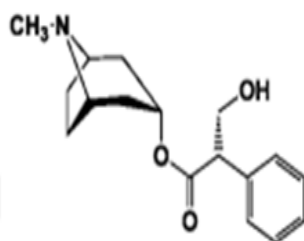
xix) Ferulic acid



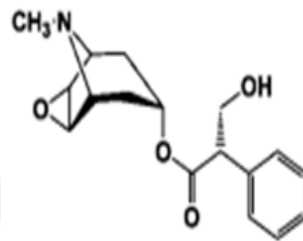
xxi) Galantamine
(*Galanthus nivalis*)



Atropine

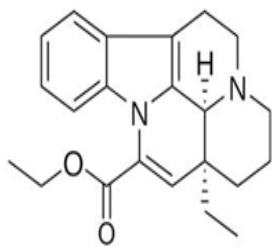


Hyoscyamine

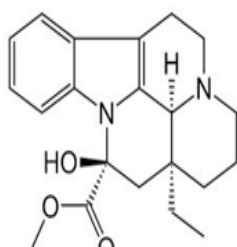


Scopolamine

xx) Tropane alkaloids (*Datura*)

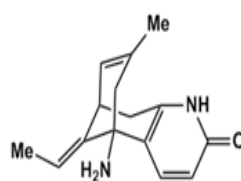


Vinpocetine



Vincamine

xxi) *Vinca minor*



xxiii) Huperzine A
(*Huperia serrata*)

Figure 1: Structures of bioactive compounds of certain nootropic herbs

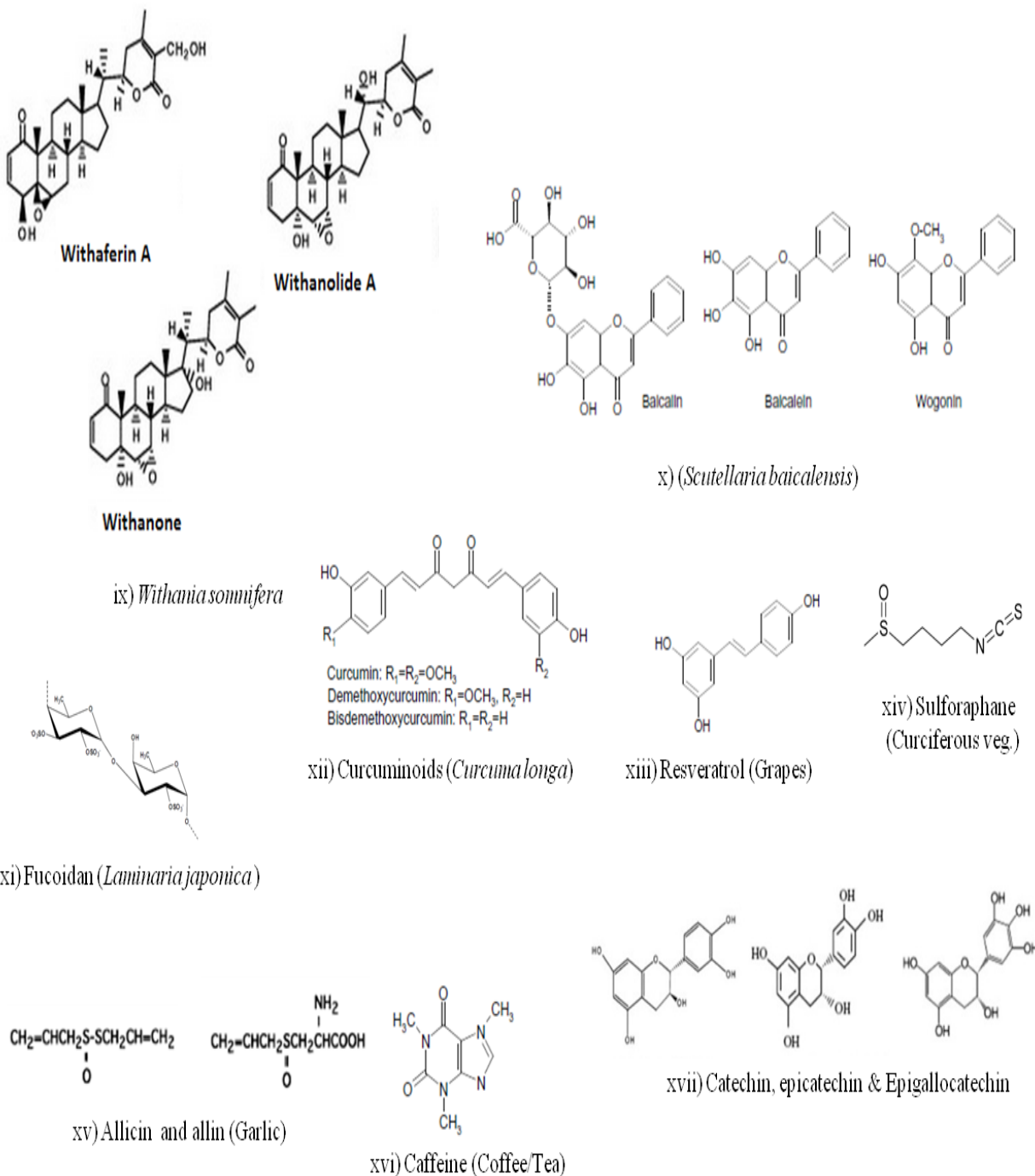


Figure 1: Structures of bioactive compounds of certain nootropic herbs

for centuries in Ayurvedic system of medicine as a *media rasayna*²⁵. Major bioactive compounds of this plant contain highly variable triterpenoid saponins, including asiaticoside, brahmoside, brahminoside, centralized, isothankunside, oxyasiaticoside, thankunside and other sapogenins. Triterpenoid acids in the plant consist asiatic acid, madecassic acid, brahmic acid, isobrahmic acid and betulic acid etc. (Figure.I-II). However, its exact mechanism of action in the treatment and management of neurodisorders has not been fully understood.²⁵

Ginkgo biloba

Ginkgo biloba (*Ginkgoaceae*) is also known as maidenhair tree, Kew tree and is indigenous to East Asia. The herb has been reported to have memory enhancing property by increase the supply of O₂, and helps to eliminate free radicals from the system thereby improving memory. Phytoconstituents include terpenoids (bilobolide, ginkgolides), flavonoids (quercetin, keampferol and isorhamnetin), steroids (sitosterol and stigmaterol) and organic acids (ascorbic, benzoic shikimic and vanillic acid). Major bioactive constituents are diterpenic lactones, ginkgolides A, B, C, J and M (Figure.I-III), and a sesquiterpenic trilactone, the bilobalide.²⁶ The leaf extract showed a neuroprotective effect against A β and nitric oxide induced toxicity.²⁷ Bilobalide and ginkgolides present in *Ginkgo biloba* have been classified as nootropic agents.²⁸ The bilobalide increased Gamma-Amino Butyric Acid (GABA) levels and glutamic acid decarboxylase activity in mouse brains.²⁸

Hypericum perforatum

It is also known as “St. John’s Wort”, the leaves are known to have bioactive compounds like, hypericin, pseudohypericin (Figure.I-IV), and related naphthodianthrones. This plant is a well known antidepressant agent in several traditional medicines and the mechanism of action initially was stated to be Mono Amine Oxidase (MAO) inhibited.²⁹

Panax ginseng

Ginseng refers to a group of several species within the *Panax* genus (*Araliaceae*) growing in north-eastern Asia, with *Panax ginseng* (Asian ginseng), among the most commonly used species in Korean and Japanese traditional medicine.²⁸ The *ginseng root* is characterized by the presence of 13 ginsenosides (triterpenic saponin complex) (Figure.I-V). It is considered to be an adaptogenic herb and able to increase the body’s resistance to various stresses like anxiety, trauma and fatigue by modulating the immune function. Ginsenosides from *Ginseng* may provide protection on

the central cholinergic system, dopaminergic system and stimulates the hypothalamus pituitary-adrenal axis.³⁰ reported that the *ginseng* extract has the ability to protect SH-SY5Y human neuroblastoma cells against MPP⁺ induced cytotoxicity and also observed ameliorative effect of ginseng water extract on various protective effects like, free radical scavenging activity, elevated Bax/Bcl-2 ratio, release of cytochrome C and activation of caspase-3 expression.

Picrorhiza scrophulariiflora

The roots of *Picrorhiza scrophulariiflora* (*Scrophulariaceae*) are rich in iridoid glycosides, terpenoids, phenylethanoid glycosides and phenolic glycosides.³¹ The dried rhizomes of *Picrorhiza* have long been used in Southeast Asia to treat neuroprotective activities. Recently, picrosides I and II (Figure.I-VI) were shown to possess neurotogenic activity. The combination of picrosides showed a significant neurite outgrowth in PC12D cells through intracellular Mitogen-Activated Protein Kinase (MAPK)-dependent signalling pathway.¹⁴

Biochemical action of neuroprotective marine algae

Marine algae is a rich source of numerous beneficial health effects. They have been identified as valuable sources of structurally diverse bioactive compounds. Numerous *in vitro* and *in vivo* studies have documented with anti-oxidant and anti-inflammatory activities of marine algae.³² *Ecklonia cava* (Phaeophyceae; Laminareaceae), also known as “sea trumpet”, has been reported to possess anti-inflammatory activity.³³ *E. cava* was also able to suppress the levels of pro-inflammatory mediators such as nitric oxide (NO), prostaglandin-E2 (PGE2) and pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α).³³ *Neorhodomela articulate* inhibited NO production, iNOS expression in interferon-gamma (IFN- γ) stimulated BV2 cells.³⁴ A number of bromophenols of *N. Ocelot* may be potential as anti-neuroinflammatory agents.³⁵ A phytochemical compound, fucoidan (Mwt. 7000 Dalton, consisting of 48% total sugar and 29% support). Isolated from *Laminaria japonica* has been reported with potent inhibitory effect against LPS-induced NO production in BV2 cells.^{36,37} successfully showed that fucoidan (Figure.1-VII) could able to protect rat cholinergic neuronal death induced by A β 1-42. Fucoidan pretreatment also blocked the activation of caspase-9 and caspase-3.³⁷ *Ulva conglobata* has been reported for its neural inflammatory, protective activity by suppression of pro-inflammatory enzyme expression such as ions and cyclooxygenase-2 (COX-2), which accounted for the

production of NO and PGE2, respectively.³⁸

Some of the phytochemicals isolated from marine algae like, decal and phlorofucofluoroecol possess memory enhancing and Acetyl Choline Esterase (AChE) inhibitory activity.³⁹ Furthermore,⁴⁰ screened several marine algae for AChE inhibitory activity and found that *Ecklonia stolonifera*, *Hypnea Valencia* and *Ulva reticulata* showed significant inhibitory activity. *Bryothamnion triquetrum* has been demonstrated to protect GT1-7 cell death produced by chemical hypoxia/aglycemia insult. The protective activity by *B. Triquetrum* seems to be due to its free-radical scavenging activity.⁴¹

Dietary sources of neuroprotective ingredients

Chronic diseases, such as coronary heart disease, diabetes, blood pressure and certain cancers are resulting from eating a diverse style, either in term of foods or food components. Importance to the dietary amino acids, melatonin and serotonin are supporting the several beneficial effects of Phyto foods associated with diet. Epidemiological studies on human populations suggest that phytochemicals in fruits and vegetables can protect against nervous system diseases. Oligomeric proanthocyanidins, naturally occurring antioxidants widely available in fruits, vegetables, nuts, seeds, flowers, roots and bark, have been reported to possess pharmacological and therapeutic activity against free radicals and oxidative stress. The grape seed proanthocyanidin extract provides significantly greater protection against free radicals and free radical-induced lipid peroxidation than vitamins C, E and β -carotene.⁴² Reported that food supplementation with blueberry, spinach, spirulina attenuated stroke-induced cerebral infarction and general locomotor impairments. People who consume greater amount of vegetables and fruits may be at reduced risk for Alzheimer diseases.⁴³ Dietary supplementation with blueberries protected dopaminergic neurons in a rat model of PD and, improved learning and memory in mouse models of AD. Pomegranate juice improved behavior deficits⁴⁴ and apple juice inhibited cognitive impairments. Flavonoids are major constituents of beverages such as wine, tea, cocoa, and fruit juices like apple, grapes, strawberries, etc. Several dietary flavonoids are the neuroprotective in nature include epigallocatechin, epigallocatechin gallate, catechin, epicatechin, condensed tannins and proanthocyanidins.

Garlic and onion has been shown to be neuroprotective, with the presence of organosulfur compounds (Allium and allacin).⁴⁵ Nuts are rich with nutrients and omega-3-fatty acids; hence the nuts may be helpful in activating the nerve

cells from undergoing degeneration. Walnuts contain the monounsaturated fatty acid such as oleic acid, linoleic acid and α -linolenic acid.⁴⁶ Peanuts are useful in neuroprotection because they contain neuroprotective Resveratrol. Berries like blueberries, blackberries, cherries and strawberries are the major source of anthocyanins such as pelargonidin, cyaniding, melvidin. Flavonoid rich blueberry reported to have inhibitory activity of nitric oxide, TNF- α and IL-1 β in activated microglia cells. Blueberries are also effective in running the age related deficits in motor function and memory enhancement by ERK pathway. Whole grains and flours are rich in fiber and known to delay the onset of dementia. Rice bran oil is rich in vitamin E (tocopherols and tocotrienols), which is excellent antioxidants and helps in neuroprotection. Bananas are super foods and contain important minerals and vitamins and possess dopamine, which is an important neurotransmitter. Homocysteine upregulation have been implicated in the destruction of the brain cells. Moreover, green leafy vegetables are rich in vitamin B, E and folate, which protect the brain by down regulating the levels of the amino acid homocysteine. Neuroprotective flavonoids such as apigenin, luteolin are found in artichoke, chives, celery and parsley. Dietary flavanones i.e. naringenin, hesperetin and taxifolin (citrus fruit and tomatoes) are observed with activation of ERK1/2 signaling in cortical neurons.

Curcumin

Curcuma longa (turmeric) is a common dietary supplement in the Indian culinary system. Several beneficial effects of curcumin for the nervous system have been reported. Curcumin (Figure.I-VII) treatment protected neurons against ischemic cell death and ameliorated behavioral deficits in experimental animal studies.⁴⁷ *In vitro* cell culture studies show that dietary curcumin is a strong dietary phytochemical for use in the prevention or treatment of age-related neurodegenerative diseases. Moreover, curcumin has been reported to reverse chronic stress-induced impairment of hippocampal neurogenesis and has the capacity to increase the expression of brain-derived neurotrophic factor (BDNF).⁴⁷ Its application also prevents the cultured rodent cortex cells against glutamate excitotoxicity.⁴⁸

Resveratrol

Resveratrol (Figure.I-VIII), a phytophenol present in red grapes, which exhibits antioxidant activity. It is known that peripheral administration of Resveratrol could able to protect neurons in the brain and spinal cord against ischemic injury⁴⁹ reported that supplementation of

Resveratrol helped to reduce ischemic damage through spinal cord neuron protection in an experimental rat model of stroke. Similarly Resveratrol can protect cultured neurons against NO mediated oxidative stress induced death. It also protected dopaminergic neurons against metabolic and oxidative insults in midbrain slice cultures of Parkinson's disease model.⁴⁹ Resveratrol protected cells against the toxicity of mutant huntingtin in worm and cell culture models.⁵⁰ Resveratrol also protected neuronal cells by amyloid β -peptide and promoted the clearance of amyloid β -peptide from cultured cells of Alzheimer's disease model.⁵¹

Sulforaphane

Sulforaphane is an isothiocyanate present in broccoli, brussels sprouts and other vegetables belonging to family Cruciferae (Figure.I-IX). Previous studies of Zhao *et al*⁵² reported that the neuroprotective effects of sulforaphane in reducing brain damage, brain edema and protective action of retinal pigment epithel. Sulforaphane has been reported to protect cultured neurons against oxidative stress and dopaminergic neurons against mitochondrial toxins.⁵³

Allium and allicin

Organosulfur compounds, such as the allium and allicin are present in high amounts in *Allium sativum* (garlic) and *A. sepi* (onions). Allium and allicin are known to have neuroprotective and free radical scavenging activities (Figure.I-X). Beside these activities, allyl-containing sulfides might activate the pathways related neuroprotection, resulting in the activation of mitochondrial uncoupling proteins.⁵⁴

Several other dietary phytochemicals have neuroprotective in nature, such as: Caffeine, a methylxanthine is the most important bioactive constituent of this beverage (coffee) providing neuroprotection (Figure.I-XI). Other similar xanthine alkaloids found in tea and chocolate are theophylline and theobromine, respectively. Tea is prepared from the leaves of *Camellia sinensis*, also native to the Old World, whereas cacao derives from the seeds of the New World species *Theobroma cacao* L. (Sterculiaceae), used by the Aztecs as medicine. Other important sources of methylxanthine alkaloids are cola nuts (genus *Cola*, Sterculiaceae family) native to Tropical Africa and used to flavor carbonated beverages, guaraná (genus *Pauline*, Sapindaceae) from South America and a popular beverage in Brazil, and Mate (genus *Ilex*, Aquifoliaceae).

Major functional groups of phytochemicals in neuroprotection

Many phytochemicals have been shown to exert a neuroprotective action in animal and cell culture models. Poly phenols (phenolic acids, anthocyanins, proanthocyanidins, flavonols, tannins), isoprenoids (sesquiterpenes, diterpenes, triterpenes, steroids, saponins), alkaloids (indole alkaloids, lysergic acid diethylamide, tropane alkaloids, ergot group) and fatty acid are active components found in many medicinal plants and regulate a variety of enzymes as well as cell receptors.⁵⁵

Polyphenols

Polyphenols are a group of plant secondary metabolites characterized by the presence of more than one phenolic unit which is linked directly to the aromatic ring. Numerous studies indicate that flavanols are of benefit for neuronal health. Catechin may protect against the brain injuries produced by endogenous neurotoxins involved in the onset of Parkinson's disease. Catechin, epicatechin and epicatechin gallate (Figure.I-XII) have also shown an ability to suppress neuroinflammation and can attenuate and inhibit activation of microglia and/or atrocities associated with the release of the mediators linked to the apoptotic death of neurons.⁵⁶ In addition, catechin derivatives may delay the onset of neurodegenerative disorders such as Alzheimer's disease through different mechanisms such as iron chelators, radical scavengers, and modulators of prosurvival genes.⁵⁶ Proanthocyanidins and condensed tannins are complex flavonoid polymers naturally present in cereals, legumes, and fruits.¹⁴ Quercetin (Figure.XIII) has been shown to protect against ischemic injury, where calcium dysregulation is one of the main instigators of neuronal cell death and brain damage. It significantly attenuates $A\beta$ -induced toxicity, protein oxidation and apoptosis in primary hippocampal cultures.⁵⁷ Indeed, treatment with quercetin reduced the spectrin breakdown products caused by ischemic activation of calcium-dependent protease cabin and inhibited the acid-mediated intracellular calcium level.⁵⁸ Some of the anthocyanins have the ability to cross the Blood-Brain Barrier (BBB) and diffuse through the central nervous system.⁵⁹ Anthocyanins have significant neuroprotective benefits in improving cognitive brain function and, defensive mechanism on oxidative stress and lipid peroxidation. There are few reports on the neuroprotective function of hydrolyzable tannins. Ellagic acid has been reported to reduce $A\beta$ - induced neurotoxicity in human SH-SY5Y neuroblastoma cells through $A\beta$ fibril formation.

The process of A β fibril formation may represent a protective mechanism of local A β clearance.⁶⁰ Ferulic acid (4-hydroxy-3-methoxycinnamic acid) (Figure.I-XI) is an ample phenolic phytochemical found in plant components and can attenuate the stress-induced behaviour in the depression-like model in mice.⁶⁰

Alkaloids

Alkaloids may affect the CNS, including nerve cells of the brain and spinal cord which control many direct body functions and the behaviour. They may also affect the autonomic nervous system, which includes the regulation of heartbeat, blood circulation and breathing. Indole alkaloids contain the indole carbon-nitrogen ring which is found in the fungal alkaloids ergine, psilocybin and lysergic acid diethylamide (LSD). These alkaloids may interfere in the action of serotonin in the brain.⁶¹ Ergot alkaloids have marked effect on blood flow, which was originally thought to be the main mechanism of action. Tropane alkaloids (Figure.I-XX) from *Datura* (atropine, hyoscyamine and scopolamine) can affect on the spinal cord and Central Nervous System (CNS). Galantamine (Figure.I-XXI) belonging to the phenanthrene chemical class, obtained from *Narcissus tazetta*, *Galanthus nivalis* and *Leucojum aestivum*. It is capable to stimulate nicotinic receptors, inhibit cholinesterase activity and further enhance cognition and memory.⁶² Vinpocetine (Figure.I-XXII) from *Vinca minor* is a highly potent vasodilator, which is useful to protect against hypoxia, ischaemia, enhancement of cerebral blood flow and glucose uptake.⁶² Isoquinoline alkaloids are highly potent analgesic and a narcotic drugs isolated from *Papaver somniferum* (opium poppy), which results in increasing Gamma Amino Butyric acid (GABA) in the synapses of the brain.⁶²

Isoprenoids

Many plant-derived essential oils, such as wormwood, have been known for anti convulsion over a century. The rhizome of valerian (*Valerian officinalis*) contains two pharmacologically active ingredients such are valepotriates and sesquiterpenes. Ortiz *et al*⁶³ reported the active effect of valerian extract on GABA (B) receptor binding property and GABA uptake inhibition in rat synaptosomes. Huperzine A, a sesquiterpene alkaloid extracted from the Chinese herb *Huperia serrata*, shows a broad range of neuroprotective properties. Huperzine A (Figure.I-XXIII) demonstrated in improved learning and spatial working memory. In *Centella asiatica* brahminoside (triterpenoid), β -pinene and γ -terpinene (monoterpenes) are active chemical substances in revitalizing and strengthening the

nervous function.

Fatty acids

The structural arrangement of neurons is crucial to their function as the cells must uphold proper electrical gradients across the membrane and be able to release and reabsorb unmetabolized neurotransmitters. Fatty acid composition of the neuronal membrane maintains a key role in the structural arrangement of neurons.⁶⁴ Consuming Mono Unsaturated Fatty Acids (MUFAs) and Poly Unsaturated Fatty Acids (PUFAs) was shown to slow cognitive decline in animals and in humans. Omega-3 and omega-6 fatty acids found in nuts, which are known to have neuroprotective activity. Numerous studies have shown that consuming diets deficient in n3 fatty acids will impair cognitive functioning. The fatty acid composition of neuronal membranes declines during aging process, however food supplementation with essential fatty acids was shown to improve membrane fluidity. In addition to affecting membrane biophysical properties, PUFAs in the form of phospholipids in neuronal membranes can also directly participate in signaling cascades to promote synaptic plasticity, neuronal function and neuroprotection.³⁵ Seabuckthorn seed oil is rich with omega-3: omega-6 (1:1) and also revealed that it has the cerebral cardiovascular functions by coordination of neurons.⁶⁵

Mechanism of action of phytochemicals with respect to neuroprotection

Phytochemicals activate cellular stress-response pathways resulting in the upregulation of neuroprotective gene products. Increasing evidence has shown that the neuroprotective effects of the neurotrophic factors are mainly mediated by inhibiting the cell death/apoptosis pathways.¹⁷ Approximately 50 neurotransmitters belonging to diverse chemical groups have been identified in the brain. Acetylcholine has been a special target for investigations because its insufficiency has been believed responsible for senile dementia and other degenerative cognitive disorders, including Alzheimer's disease. Phytochemicals can activate the transcription factor NF- κ B by inducing the expression of antioxidant enzymes and Bcl-2. Some phytochemicals can activate multiple signalling pathways by ligands that bind to various receptors like G-Protein-Coupled Receptors (GPCR), Growth Factor Receptors (GFR) and Insulin Receptors (IR). These receptors activate kinase cascades which involve Protein Kinase C (PKC), Mitogen-Activated Protein Kinases (MAPK) and Phosphatidylinositol-3-Kinase (PI3K). Flavonoids activate ERE-CREB pathway and the P13 kinase-mTOR cascade

leading to changes in synaptic plasticity.

Phytochemicals including isothiocyanates, insoles, terpenes, diallyl sulfides, curcuminoids and cytokines have been shown to activate one or more pathways upstream of nuclear factor erythroid 2-related factor 2 (NRF2). Ellison activates Transient Receptor Potential (TRP) ion channels in the plasma membrane of neurons, resulting in Ca^{2+} influx, which activates neuroprotective kinase cascades via Mitogen-Activated Protein Kinases (MAPK), Camp-Response-Element-Binding protein (CREB)⁵⁴; CREB induces the expression of Brain-Derived Neurotrophic Factor (BDNF). BDNF is a major neurotrophic factor, which can initiate MAPK/ERK and PI-3K/Akt pathways, through binding to its tyrosine kinase TrkB receptor and thus activate the downstream molecules which can promote neurogenesis and cell survival.⁶⁶ Allyl-containing sulfides might activate other pathways related to stress, resulting in the upregulation of mitochondrial uncoupling proteins.⁵⁴

Flavanones, such as hesperetin and its metabolite, 5-nitrohesperetin, have been observed to inhibit oxidant-induced neuronal apoptosis via a mechanism involving the activation/phosphorylation of signalling proteins important in the pro-survival pathways. Capsaicin activates specific Ca^{2+} channels (vanilloid receptors). A wide range of phytochemicals such as flavonoids, terpenes, and related substances are known to influence the function of ionotropic receptors for GABA, the major inhibitory neurotransmitter in the brain.⁶⁷ Such GABA modulators have been found in fruits, vegetables, various beverages, and herbal extracts such as *Ginkgo biloba* and *Ginseng*.

CONCLUSION

Many lifestyle factors endorse health of the nervous system in trouble by imposing a mild stress on neural cells. Phytochemicals in the form of dietary supplements, herbs and spices, comprise an unlimited source of molecules available for improving human health. It is likely that different phytochemicals produce *in vivo* additive and/or synergistic effects, thus amplifying (or reducing/inhibiting) their activities. Many of the phytochemicals have recently been reported to exert neuroprotective effects in various experimental models of neurological disorders. The information collected in this review on a large number of herbal extracts and constituents that possess therapeutic effects in animal models/*in vitro* cell culture models of neurological disorders may be used in a search for novel pharmacotherapies from medicinal plants

for these illnesses.

The pharmacological actions of many phytochemicals and herbal extracts involve to some extent the mechanisms known to be responsible for convening neuroregeneration actions. For example, several anxiolytic agents have the capacity to enhance the inhibitory function of central GABA receptor. Many herbal antidepressant agents have the ability to inhibit MAO activity and modulate monoaminergic neurotransmission. Antidementia effects of many herbal agents are related to the inhibition of AChE activity. On the other hand, a considerable number of herbal extracts and constituents, most notably antidepressant and antidementia agents, possess antioxidant and neuroprotective actions, as evidenced by the protection against neuronal cell death induced by exposure to excessive free radicals, excitatory toxins, toxic derivatives of amyloid precursor protein, and other neurotoxins.

Although demand for phytotherapeutic agents is growing, there is a need for their scientific validation before plant derived extracts gain wider acceptance and use. Hence “natural” products may provide a new source of beneficial neuropsychotropic drugs. These studies provide a phytochemical basis for some of the effects that these herbal preparations have on brain function and neuroprotection. As implicitly outlined in this review, most of our current knowledge about CNS-active plants of cultural and traditional importance arose from ethnobotanical and ethnopharmaceutical studies, as for other natural active ingredients.

CONFLICT OF INTEREST

The authors have no conflict of interest

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