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Neuroprotective Plants: A Review

Hrishikesh Chaturvedi & Amit Kumar

Department of Pharmacy, Sunrise University, Alwar, Rajasthan

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Corresponding author: Hrishikesh Chaturvedi

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Abstract:

Enhanced oxidative stress in the central nervous system (CNS) is a consequence of an overactive metabolism and an inadequate antioxidant defence mechanism. More and more evidence from experiments suggests that reactive oxygen species (ROS) have a role in neurodegenerative diseases. The term "neuroprotection" describes measures taken to keep neurones' structures and functions intact in the face of threats from cellular damages brought on by various chemicals or neurological illnesses. Several neurodegenerative diseases, such as schizophrenia, depression, Alzheimer's disease, dementia, cerebrovascular impairment, seizure disorders, parkinsonism, and head injuries, may severely limit a person's ability to operate. These disorders may be reduced or avoided with the use of antioxidants, which inactivate them. The ancient Indian medicinal practice of Ayurveda has linked the antioxidant and neuroprotective effects of some plants to a range of health benefits. An ancient medical system known as Ayurveda has found a number of plants that have antioxidant and therapeutic effects on neurological diseases. Research has shown that extracts from Bacopa monniera may boost cognitive function in humans. Bacopa extract has antioxidant qualities, according to reports. Research has shown that ginkgo biloba may reduce free oxygen radical levels. Withania somnifera extracts improve antioxidant status in oxidative stress-induced neurodegeneration. It is still need to investigate many more plants to see whether they possess any neuroprotective properties. According to the study, many of the medicinal plants used in Ayurveda and Chinese medicine have a wide range of components and phytochemicals that may have a neuroprotective effect. This might be useful in the treatment of neurodegenerative and neuropsychiatric diseases.

Keywords: Neuroprotection; Antioxidant; Neurodegenerative disease; Medicinal herbs.

INTRODUCTION

A variety of neuropsychiatric and Alzheimer's disease disorders, including Alzheimer's disease, anxiety, cerebrovascular impairment, seizures, Parkinson's disease, and others, can cause neuronal loss. To protect the Central Nervous System (CNS) from this loss, neuroprotection techniques and their significance mechanisms are utilised. According to projections, neurodegenerative illnesses will overtake cardiovascular disease as the leading cause of mortality

among the elderly in the coming decades [1]. One of the neuroprotection strategies that has shown promise is the use of phytochemicals as a potential treatment for neurodegenerative diseases. In spite of the fact that both natural and synthetic neuroprotective drugs have been seen, the latter are believed to cause side effects such dry mouth, fatigue, drowsiness, sleepiness, anxiety, unease, problems with balance, and so on. In recent years, there has been a lot of focus on herb-based medicinal products from both academic institutions and businesses on a global scale. Therefore, phytochemicals' ability to modulate neuronal activity and provide protection against neurodegeneration has been the subject of a great deal of study. Phytotherapy, or herbal medicine, is an ancillary and alternative form of healthcare that makes use of the curative properties of plants and their various parts.

It is difficult to determine which portion of the herb has biologically active compounds for specific discussion since herbal products often include a wide array of bioactive phytochemicals. Herbalists from all over the world are on the hunt for bioactive phytochemicals that have neuroprotective properties in traditional medical systems (e.g., those of China, India, Korea, the Mediterranean, etc.). Herbal remedies from various traditional medicine systems will be discussed in this review, along with the bioactive phytochemicals found in them and the effects they may have on neuroprotective function and other ailments [2]. The gradual death of neurones due to an underlying neurodegenerative disease is known as neurodegeneration [3]. The deterioration of a functionally or physically related cluster of neurones is a hallmark [4]. Neurobiological tissue deteriorates with neurodegeneration. Neurodegenerative diseases such as Alzheimer's, Parkinson's, and cognitive impairment result from neuronal degradation that goes unrepaired. Cranial nerve degeneration and Amyotrophic lateral sclerosis. Accordingly, the effects of any disease process leading to neuronal death are often permanent [5]. Because of people living longer, neurodegenerative diseases have become one of the most important areas of medical study. A broad phrase, "neuroprotection" encompasses any therapeutic approach that uses an intervention, such a medication or therapy, to stop the death of nerve cells, or neurones. This mechanism prevents the acute illness from further damaging or degenerating cells in the central nervous system. The goal of neuroprotection is to preserve the brain's cellular connections in order to prevent damage-induced neuronal dysfunction and maintain normal neural function. Numerous neuroprotection medicines are either already on the market or are in the development phase. Since many of the underlying mechanisms are similar, several of these drugs may have applications in more than one condition.

Neurodegenerative diseases

The central and peripheral nervous systems are equally impacted by neurodegenerative disorders (NDs), which are anomalies of the central nervous system that worsen with time. Neurodegeneration may develop when brain cells die off one by one over time. In order for neurodegeneration to begin, peroxidation by means of reactive oxygen species (ROS) and nitrogen species (RNS) must occur. It is recognised that neuroinflammation plays a role in the aetiology of several neurodegenerative diseases. National Institute of Neurological Disorders and Stroke statistics show that over 600 neurological disorders have been diagnosed worldwide [6]. This review delves further into a few of them.

Alzheimer's disease

Symptoms of this neurodegenerative condition include a decline in cognitive abilities, the gradual deterioration of neurones, and the development of neurofibrillary tangles and amyloid-β plaques. It starts with damage to synapses and eventually leads to the death of neurones [7]. This is the most typical presentation of adult ADD and dementia [8]. Medication that elevates one's mood, memory, and conduct is known as a cognitive enhancer. Late in life, often between 60 and 70 years of age, patients with sporadic forms of Alzheimer's disease sometimes acquire the condition [9].

Parkinson's disease (PD)

A degenerative movement condition that affects the nigrostriatal area and causes a gradual death of dopaminergic neurones. Some of the clinical signs of this complex condition include motor impairments such rigidity, postural instability, bradykinesia, resting tremor, and gait problems [10]. One major obstacle to developing neuroprotective medications is our current knowledge of the illness variables that cause dopaminergic neurone death. It is believed that environmental factors, genetics, or a combination of the two contribute to this clinical condition, although the specific metabolic enzymes responsible for it remain unknown.

Anxiety

Cognitive, physiological, emotional, and behavioural aspects all come together to form anxiety, a disorder that affects both the mind and the body. It has the potential to worsen to the point that it becomes a source of anxiety for the sufferer, interfering with even their most basic daily tasks. A total of seven clinical conditions are included in anxiety disorders [11]:

a) Generalized Anxiety Disorder (GAD): In this state, the person will be plagued with continual anxiety and worry, and will become unduly preoccupied with trivial concerns.

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: Fear and anxiety are evoked by a specific stimuli or scenario.

d) Agoraphobia: is the fear of being in a location or circumstance where escaping is difficult or embarrassing, or when aid may be unavailable.

e) Social Anxiety Disorder (SAD): It is a strong apprehension of negative public scrutiny, as well as public disgrace or humiliation.

f) Obsessive-Compulsive Disorder (OCD): It is characterised mostly by reoccurring obsessions and compulsions.

g) 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.

h) Separation anxiety disorder: It is the perception of inappropriate or excessive worry caused by being distanced from a location or person. Monoamines (dopamine, noradrenaline, and serotonin), neuropeptides (galanin, neuropeptide Y, arginine vasopressin, tackykinin), neurosteroids, and cytokines have all been found to have a role in anxiety modulation.

Depression

A low mood and an overwhelming feeling of melancholy are what the word "depression" describes. One of the most common mental illnesses, depression may range from a

moderate sadness to overwhelming despair. Both internal and external variables impact the frequency of depressive symptoms and the severity of mood swings. The World Health Organisation (WHO) estimates that 455 million people are now dealing with a mental or behavioural disease, and this number is expected to rise substantially by 2020. According to a World Health Organisation report, depression is among the top 10 leading causes of death and disability globally. Some of the neuronal structural alterations that occur in depressive states include a shrinkage of the prefrontal cortex and hippocampus, dysfunctions of the HPA axis, and anomalies in 5-HT and its receptors. It is well-known that schizophrenia and anxiety are neurological disorders characterised by dysregulation of the 5-HT monoaminergic neurotransmitter. [12]

Epilepsy

Nearly half a billion people throughout the globe suffer from epilepsy, making it the most prevalent neurological illness. Periodic epileptic seizures, characterised by the recurrent involuntary contraction of striated muscle, are a hallmark of this disorder. The frequency and severity of these seizures may be somewhat unpredictable. The rapid and excessive firing of neurones in the brain's grey matter is the root cause of seizures. Potential causes of neuronal injury and cell death in epilepsy include abnormalities in voltage-sensitive sodium and calcium channels, problems with GABA-mediated inhibition, and an excess of glutamate-mediated neurotransmission [13].

Schizophrenia

Among mental diseases, it ranks high in significance. Patients with this illness are currently unaware of what is occurring. This condition manifests in two distinct ways :

1. Positive symptoms include delusions, hallucinations, cognitive problems, and deviant conduct.
2. Negative symptoms include social withdrawal and flattening of emotional reactions.

In this situation, neurotransmitters such as dopamine, 5-HT, acetylcholine, and norepinephrine levels in the brain increase [14].

Mechanism of neurodegeneration excitotoxicity

'Excitotoxin' was used to describe the neurotoxic effects of excitatory amino acids that damaged neurones at the injection site [15]. Neuronal death caused by activation of receptors for excitatory amino acids is known as excitotoxicity. In the brain and spinal cord, glutamate acts as the principal excitatory neurotransmitter. The interaction of glutamate with certain membrane receptors mediates several brain functions, including as thinking, remembering, and emotion. Glutamate is thought to mediate the vast majority of excitatory synaptic transmission in the brains of mammals. Glutamate receptor activation has the potential to cause neuronal damage and death in several neurodegenerative diseases. It seems that this kind of injury is brought on by an overabundance of calcium entering neurones via ionic channels that are triggered by glutamate receptors. While glutamate is essential for proper brain function, it may induce cell death via an excitotoxic mechanism when levels are too high [16].

Apoptosis:

Multiple cell signals may trigger apoptosis, which is characterised by alterations in the nucleus, such as chromatin aggregation, DNA fragmentation, and cell shrinkage. It is often linked to excitotoxicity. At the end of cell death, proteases are activated, which

activates a number of proteins that were previously inactive [17].

Amyloid cascade hypothesis:

The loss of neuronal cells is caused by the irregular deposition of β-amyloid, according to this concepts. There is evidence that a fatal chemical cascade in neurones is triggered in people with abnormalities of the DNA coding Amyloid Precursor Protein (APP). According to reference 18, APP that is changed due to abnormal DNA eventually builds up as deposits of β amyloid.

Oxidative stress:

Oxygen is a partner that might be harmful. Oxidative stress may harm cells and tissues, according to the available research. Nevertheless, oxidative stress results in free radicals, which are involved in both healthy and unhealthy human metabolism. Enzymatic events occurring in living organisms may produce oxygen radicals. These byproducts are present in neurodegeneration and the ageing process, and oxidative stress is a lethal effect of them. During oxidative stress, the balance between pro- and anti-oxidants might tip in favour of the pro-oxidants due to an increase in oxidative metabolism. Alcohol, colds, narcotics, stress, toxins, radiation, and many other things may trigger its cellular proliferation. Oxidative stress occurs when a biological system's antioxidant capacity is overwhelmed by the production of free radical moieties [19].

Sodium nitrite mediated neurodegeneration

$NaNO_2$ nitrite salt (Sodium nitrite) has the capacity to convert haemoglobin to methemoglobin. This reduces blood oxygen carrying capacity, resulting in memory impairment. Under clinical conditions of AD, the combination of $NaNO_2$ and D-galactose has also been reported **[20]**.

Antioxidant Defense

An antioxidant is any chemical that, when present in low quantities relative to an oxidizable substance, considerably delay or prevents the oxidation of that substrate [21]. These antioxidants may be endogenous or exogenous in origin. Depending upon mode of action, antioxidants may be classified as chain breaking and preventive antioxidants. The enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSHPx), which form the principal intracellular antioxidant protection mechanisms by eliminating superoxide anion and hydrogen peroxide, are among the most notable defences. There has been evidence that phytochemicals that antioxidant characteristics alleviate the symptoms of neurodegeneration. According to certain investigations, phenolic compounds such as flavonoids are enormously potent antioxidants [22]. Flavonoids have the ability to scavenge free radicals while also minimizing lipid peroxidation [23].

Herbal neuroprotection

Ayurveda, an Indian practice of medicine, is gaining popularity these days. Ayurveda's illness prevention and health promotion strategy is becoming more popular. The revitalization and rejuvenation treatment therapy in Ayurveda is known as the 'Rasyana chikitsa'**.** *Rasayana* medications have been discovered to be a rich source of antioxidants and function inside the human body by altering the nuero- endocrino-immune systems [24, 25]. These medicinal plants provide a large untapped reservoir of pharmaceuticals, and the structural variety of their component components makes them an excellent source of potential lead compounds [26]. Certain non-nutritive elements in plants, such as terpenoids and also contain flavonoids, have been shown in studies to have antioxidant capabilities. A

increasing interest in traditional remedies may be explained by a lack of effective and universally applicable pharmacological medications in current therapy for neurodegenerative illnesses [27]. According to WHO estimates, 70-80% in consideration of the world's population relies on traditional medicine, primarily plant drugs, for basic healthcare. The conventional crude method of treatment has given way to standardized plant extracts, formulations, and even composite medicines [28].

Traditional herbs for neuroprotection.

Bacopa monniera

"Brahmi" has been used for millennia in the Ayurvedic school of of medication as a brain booster for learning, memory improvement, and an anti-stress agent in anxiety [29]. It includes a variety of bioactive phytochemicals, including herpestine (alkaloids), d-mannitol, hersaponin, and monnierin (saponins). Numerous bacosides and bacopasaponins have been discovered as major active components. Bacosides A and B are the substances responsible for Bacopa's cognitive abilities effects [30]. Bacosidescontribute in the healing of injured neurons by increasing neuronal synthesis, kinase activity, synaptic activity restoration, and nerve impulse transmission.

Centella asiatica

Centella asiatica, a species of the Apiaceae (*Umbelliferae*) family, is a psychotropic medicinal plant that has been used for ages as a medium rasayna in the Ayurvedic school of medicine. This plant's main bioactive constituents are extremely variable triterpenoid saponins such as asiaticoside, brahmoside, brahminoside, centralised, isothankunoside, oxyasiaticoside, thankunoside, and other sapogenins. Triterpenoid acids found in plants include asiatic acid, madecassic acid, brahmic acid, isobrahmic acid, and betulic acid, among others. However, its precise mechanism of action in the treatment and management of neurodisorders remains uncertain [31].

Ginkgo biloba

Ginkgo biloba (Ginkgoaceae) is also known as maidenhair tree, Kew tree and is indigenous to East Asia.

The herb has been suggested to have memory boosting properties by increasing the availability of O2 and aiding in the elimination of free radicals from the system, therefore improving memory. Terpenoids (bilobolide, ginkgolides), flavonoids (quercetin, keampferol, and isorhamnetin), steroids (sitosterol and stigmasterol), and organic acids are examples of phytoconstituents (ascorbic, benzoic shikimic and vanillic acid). Major bioactive constituents are diterpenic lactones, ginkgolides A, B, C, J and M, and a sesquiterpenic trilactone, the bilobalide [32]. The leaf extract showed a neuroprotective effect against Aβ and nitric oxide induced toxicity [33].

Bilobalide and ginkgolides present in *Ginkgo biloba* have been classified as nootropic agents. The bilobalide increased Gamma-Amino Butyric Acid (GABA) levels and glutamic acid decraboxylase activity in mouse brains [34].

Hypericum perforatum

It is also known as “St. John’s Wort”, the leaves are known to have bioactive compounds like, hypericin, pseudohypericin, and related naphthodianthrones. This plant is a well-known antidepressant ingredientin numerous traditional remedies, with the first mechanism of action being Mono Amine Oxidase (MAO) inhibition [35].

Panax ginseng

Ginseng *(Panax ginseng)* Ginseng refers to a collection of many Panax genus (*Araliaceae*) plants grown in north-eastern

Asia, with Panax ginseng (Asian ginseng) being one of the most extensively treated species in Korean and Japanese traditional medicine [34]. *The ginseng root* is characterized by the presence of 13 ginsenosides (triterpenic saponin complex). It is recognized as an adaptogenic herb, capable of increasing the body's resilience to different stressors such as anxiety, trauma, and exhaustion by altering immunological function. Ginseng ginsenosides may protect the central cholinergic and dopaminergic systems, and other activate the hypothalamus pituitary-adrenal axis [36], observed that ginseng extract may protect SH-SY5Y human neuroblastoma cells from MPP+-induced cytotoxicity and that ginseng water

extract can improve numerous protective properties such as free radical scavenging activity, raised Bax/Bcl-2 ratio, cytochrome C release, and caspase-3 activation.

Picrorhiza scrophulariiflora

The roots of *Picrorhiza scrophulariiflora* (*Scrophulariaceae*) are rich in iridoid glycosides, terpenoids, phenylethanoid glycosides and phenolic glycosides [37]. Picrorhiza rhizomes have traditionally been applied in Southeast Asia to treat neuroprotective properties. Recently, picrosides I and II are said to have neuritogenic action. The combination of picrosides showed a significant neurite outgrowth in PC12D cells through intracellular Mitogen- Activated Protein Kinase (MAPK)-dependent signaling pathway [38].

Conclusion

Plants, in the form of herbs, are an infinite source of molecules that may be used to improve human health. A single plant, on the other hand, has countless of secondary, bioactive metabolites, a chemical diversity that has distinguished plant evolutionary success and benefited in their adaptation to changing climates. Several phytochemicals that have lately been discovered to have neuroprotective benefits in various animal models of neurological illnesses had previously been proven to have cytostatic or cytotoxic effects on cancer cells. Although the demand for phytotherapeutic drugs is increasing, scientific confirmation is required before plant-derived extracts may be widely accepted and used. Some of the benefits of these herbal remedies on brain function and neuroprotection are now supported by a phytochemical foundation, according to these researches. Furthermore, a critical quality for a promising therapeutic drug is its capacity to pass the blood-brain barrier and reach CNS target areas.

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