

Neuroprotective Activity of Herbal Medicinal Products: A Review

Irfat Ara

Research officer, Regional Research Institute of Unani Medicine, Srinagar, Jammu and Kashmir, India

Mudasir Maqbool

Research Scholar, Department of Pharmaceutical Sciences, University of Kashmir, Srinagar, Jammu and Kashmir, India

Imran Gani

Research Scholar, Department of Pharmaceutical Sciences, University of Kashmir, Srinagar, Jammu and Kashmir, India

Plant-based drugs are among the earliest pharmaceuticals documented in even the most basic medical system's history. They are the most often used medicines due to their wide acceptance and general perception of their safer profile as compared to conventional drugs. Herbal medicines and products are gaining popularity around the world, not just as a caffeine-free alternative, but also as dietary supplements for low-calorie diets. In recent years, traditional medicine has gotten increased attention. Traditional medicine uses a range of herbs to cure neurodegenerative disorders such as Alzheimer's and other similar central nervous system issues. The term "neuroprotection" refers to strategies and systems for preventing neuronal injury in the central nervous system (CNS). Humans still have access to nature's medicines. Many important drugs are obtained from natural sources or based on the structural characteristics of naturally occurring substances, such as vincristine, artemisinin, and gentamicin. Traditional medicine has been documented to use a number of natural substances, usually plant extracts, for neuroprotective, memory-enhancing, and anti-aging objectives. Such plants include Panax ginseng, Ginkgo biloba, Bacopa monnieri, Curcuma longa, and Salvia officinalis. These plants were studied to see if the traditional claim was true, as well as to learn more about the mechanism through which they give neuroprotective advantages.

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Introduction

Traditional herbal remedies were known before the advent of modern scientific approaches to healthcare and are still used by the majority of the population today. The development of a wide range of synthetic medicines, now widely used to treat mild colds and coughs, cancer and central nervous system problems, has undoubtedly influenced the plant natural products (CNS). Written records and the use of medicinal herbs date back 5000 years. When Friedrich Bayer & Co. brought synthetic acetylsalicylic acid, commonly known as aspirin, a safer synthetic form of salicylic acid, a key component of willow bark, to the world in 1897, the strong traditional links between nature and human health began to unravel. Plant-based medicines are among the earliest medicines documented in the history of even the most basic medical system. They are the most commonly used drugs due to their ubiquitous availability and the widespread perception that they have a safer profile than synthetic drugs. Herbal medicines and products are becoming increasingly popular around the world, not only as a caffeine-free alternative, but also as a dietary supplement for a low-calorie diet [1]. It is estimated that medicinal plants currently make up a significant part of the US pharmaceutical sector. Much of our current pharmacology is based on knowledge we have gained from a long history of using therapeutic plants or their bioactive components. Aspirin, digitalis,

morphine and quinine, all commonly used in allopathic medicine, were first extracted from herbal compounds. Later, as chemistry and biochemistry advanced, as did the development of isolation, separation, and biosynthetic techniques, many drugs were separated and evaluated for bioactivity. Most plant compounds have been synthesized thanks to advances in organic biochemistry. However, plants continue to provide some of the most important medicines with basic raw materials, but the production of new medicines from synthetic sources has shown tremendous improvements, and antibiotics are emerging as preeminent therapeutics [2-5].

Significance of medicinal herbs

More than 75% of the population uses herbs as traditional medicine, according to the World Health Organization. Medicinal herbs are a potential source of medicines that are of significant importance to the health of people and animals around the world in bad circumstances, as well as maintaining health. The Indian herbal industry has studied these Ayurvedic herbs which are now processed into numerous herbal formulations and through a study in ethano-Pharmacology and Traditional Medicine they have been included in the International Pharmacopoeia with extensive research in the fields of pharmaceuticals, photochemistry, pharmacology and clinical therapy [6-9]. As a result, the growth of research on medicines from natural sources has now shifted from herbal shops to drug research labs, resulting in remarkable research in various branches of pharmaceutical science using Ayurveda literature, which has helped the herbal industry in India grow by 20% annually [10-14].

Importance of immune herbs: Immunomodulating herbs encompass the intrinsic and adaptive arms of the immune response, affecting a specific or nonspecific aspect of the immune response. Among other things, they are vital in the case of immune deficiency, infections, inflammation and cancer. Immune herbs are known to act on cytokines, interleukins, lymphocytes and other cells, but also can act as an immune adjuvant, immunosuppressant or suppressant that enhances the effectiveness of the vaccine by acting on cellular immunity and the body's resistance through its action on the two immune cells increased responses [15-20].

Idea of Ayurveda: Traditional herbs have thrived in one form or another in various cultures and societies around the world. For thousands of years, the use of these natural herbs in various treatments has been practiced in the ancient Indian system of medicine known as Ayurveda. Ayurveda, Yoga, Unani, Homeopathy, Naturopathy and Siddha have been widely practiced in Indian culture for thousands of years. Ayurveda, India's oldest and most influential tradition, is based on philosophy and experimentation. Ayurveda is available in various regional languages and maintains a database of a number of therapeutic herbs with a focus on enhancing the host's immune system [6, 21-24]. Ayurveda is believed to mention 1200 ailments in various classical texts. Atharveda (ca. 1200 BC), Charak Samhita and Sushrat Samhita (1000-500 BC) serve as a collection of 700 medicinal herbs. The Ayurvedic system, composed of traditional medicine, offers a wide range of plants with activities such as immune stimulation, neurostimulation, tonic, antibacterial, antiaging, antirheumatic, anticancer, antiviral and adaptogen, among others, as Source for alternative medicine, new drugs and health products [22, 25-27]. **Neuroprotection:** the term neuroprotection implies the preservation of neuronal structure and/or function. Neurodegenerative diseases, stroke, traumatic brain injury, spinal cord injury, and acute neurotoxic treatments are all being studied with this therapy. Neuroprotection aims to stop or reduce the loss of neurons in order to avoid or limit the progression of the disease and the resulting damage. Regardless of the symptoms or trauma associated with the CNS, many of the underlying causes of neurodegeneration remain the same. Oxidative stress, mitochondrial dysfunction, excitotoxicity, inflammatory disorders, iron processing, and protein aggregation are the same common pathways. Neuroprotective treatments often target oxidative stress and excitotoxicity, two factors closely associated with CNS disorders. Not only can oxidative stress and excitotoxicity induce neuronal death alone, but they can also have synergistic effects that cause even more degeneration when combined. As a result, a major component of neuroprotection is limiting excitotoxicity and oxidative stress. Glutamate and antioxidant antagonists are two typical neuroprotective drugs to minimize

excitotoxicity and oxidative stress [28-32].

Excitotoxicity: One of the most common pathways for cell death in CNS diseases is glutamate excitotoxicity. Due to the lack of selectivity of the glutamate-binding ion channel, overstimulation of glutamate receptors, particularly NMDA, increases calcium ion flux. Buffer levels of Ca^{2+} sequestration with mitochondria are exceeded when Ca^{2+} accumulates in the neuron with significant neuronal effects. Ca^{2+} is a second messenger that controls a variety of downstream processes. Excess Ca^{2+} leads to improper control of these activities, ultimately leading to cell death. Neuroinflammation is an integral part of many CNS disorders and is thought to promote Ca^{2+} [5, 32-37].

Glutamate antagonists: Glutamate antagonists are the most common treatment for excitotoxicity in CNS disorders and they help prevent or treat it. The purpose of these antagonists is to prevent the buildup of Ca^{2+} and hence excitotoxicity by inhibiting the binding of glutamate to NMDA receptors. Many glutamate antagonists have been studied as potential treatments for CNS disorders, however many have proven ineffective or caused severe side effects [14, 20, 38]. Few treatments which have proved potential in the future are the following:

Ø **Estrogen:** 17-estradiol restricts NMDA receptor and other glutamate receptors that contribute to the regulation of excitotoxicity [39].

Ø **Ginsenoside Rd:** ginsenoside Rd, according to the research, inhibits glutamate excitotoxicity. Clinical trials in people who have had an ischemic stroke have revealed that the drug is both effective and noninvasive [33].

Ø **Progesterone:** it is well known that progesterone can help avoid subsequent damage in people with traumatic brain injury and stroke [36].

Ø **Simvastatin:** simvastatin has been demonstrated to have substantial neuroprotective effects in Parkinson's disease models, including anti-inflammatory effects due to NMDA receptor regulation [38, 40].

Ø **Memantine:** memantine reduces NMDA-induced excitotoxicity while keeping some NMDA signaling as a noncompetitive low affinity NMDA antagonist [40].

Oxidative stress: Increased oxidative stress can be the result of neuroinflammation, which is a known component of cerebral ischemia and numerous neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), and Amyotrophic lateral sclerosis (ALS). Because of their role in triggering cell death, higher levels of oxidative stress are often addressed in neuroprotective drugs. Oxidative stress can either destroy neurons directly or initiate a chain reaction leading to misfolded proteins, mitochondrial dysfunction, proteasomal dysfunction, or activation of glial cells [27, 31, 41].

Antioxidants: The most common treatment to reduce oxidative stress is to increase antioxidant levels. Antioxidants work by ridding the body of reactive oxygen species, which are the main cause of neurodegeneration. Some popular antioxidants that help reduce oxidative stress are

Ø **Acetylcysteine:** In the pathophysiology of a number of neuropsychiatric disorders, acetylcysteine affects glutamatergic transmission, neurotrophins, the antioxidant glutathione, apoptosis, mitochondrial activity, and inflammatory pathways [42, 43].

Ø **Crocin:** it is a saffron derivative discovered to be a powerful antioxidant for the brain [44-46].

Ø **Estrogen:** the antioxidants 17-estradiol and 17-estradiol have been shown to be beneficial. These drugs have immense potential. The nonestrogenic stereoisomer of 17-estradiol is 17-estradiol [47].

ØFish Oil: polyunsaturated n-3 fatty acids found in fish oil have been shown to protect against oxidative stress and mitochondrial dysfunction [48].

ØMinocycline: the semisynthetic tetracycline minocycline can cross the blood-brain barrier. In Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), and Amyotrophic lateral sclerosis, minocycline has been shown to provide neuroprotective benefits in the CNS [49, 50].

ØPQQ: pyrroloquinoline (PQQ) is a neuroprotective antioxidant that works in multiple ways. Resveratrol protects against oxidative stress by reducing hydrogen peroxide-induced cytotoxicity as well as cellular reactive oxygen species (ROS) accumulation. It has been shown to protect against a range of neurological disorders [51, 52].

Other stimulants, at the right amounts, can help protect the brain [53-55]:

ØSelegiline: in the early stages of Parkinson's disease, it has been found to reduce disease progression and delay the onset of disability by an estimated 9 months in Parkinson's disease.

ØNicotine patches are also available in the market. Caffeine: caffeine has been shown to protect against Parkinson's disease.

ØCaffeine promotes cysteine absorption in neurons, leading to glutathione production and neuroprotection.

Other neuroprotective treatments

There are a variety of neuroprotective therapies available that target distinct pathways of neurodegeneration:

Caspase Inhibitors: caspase inhibitors are widely used and researched for their apoptotic effects [56].

ØTrophic Factors: the role of trophic factors in CNS diseases, particularly ALS, will be investigated. CNTF, VEGF, IGF-1 and BDNF are all potential neuroprotective trophic factors [57].

ØAntiprotein aggregation agents: neuron cell death is known to be caused by protein aggregation. Antiprotein aggregation drugs may be helpful. Whether this can be eliminated as the cause of neurodegeneration is being tested with various treatments. These include sodium, trehalose, poly-Q binding peptide and sodium 4-phenylbutyrate [58].

ØTherapeutic hypothermia: it is being researched as a possibility for neuroprotective therapy in traumatic brain injuries and is intended to reduce intracranial pressure [59].

ØErythropoietin: erythropoietin has been observed to protect nerve cells from hypoxia-induced toxicity.

ØLithium: it inhibits glycogen synthase kinase-3 (GSK3), modulates neurotrophins and growth factors (e.g. BDNF), regulates inflammatory molecules, modulates neuroprotective components e.g. B-cell lymphoma-2 (Bcl-2) and heat shock protein-70 (HSP-70) and inhibits proapoptotic factors.

Promising herbal drugs for neurodegenerative disorders treatment:

ØHypericum perforatum: it is used worldwide as an herbal medicine for depression and related illnesses. A comprehensive analysis found that plant extracts were extremely effective in treating depressive disorders [37, 60].

ØGinkgo biloba: *G. biloba* is considered by many people to be a living fossil. *Ginkgo biloba* is one of the oldest tree species in the world. The tree only survived the cold period in Asia before being introduced to Europe and America as an ornamental tree in the 18th century. As a vasodilator, an extract from the green leaves of the plant has been shown to be effective in treating peripheral circulatory problems. After observations in patients and experimental animals, this extract, known as Egb761, was discovered to be a CNS function altering and neuroprotective drug. It could be used to treat patients with cerebral insufficiency or cerebrovascular diseases. In Europe, ginkgo is used extensively to treat dementia. It contains 11 flavonoids that act as antioxidants and help blood flow in the brain. Despite several clinical studies proving to be scientifically flawed, ginkgo has been shown to improve thinking, learning, and memory. It has proven to be very effective in Alzheimer's patients. The therapeutic properties of ginkgo are based on the synergistic effects of its components, which are currently unknown [61, 62].

ØBacopa monniera: also known as Brahmi. In India it is also known as Jalbrahmi or Nirbrahmi. It contains Brahmin and herpestine alkaloids, as well as D-mannitol and saponins, as well as bacosides A and B. The herb is used as a nerve tonic, diuretic, and antibiotic in the treatment of asthma, epilepsy, folly, and headaches. It is a crucial component in the formulation of Medhya Rasayana that aids in learning and memory. The effect of 50% ethanol extract from whole plant without roots was first shown in tests using 50% ethanol extract from whole plant without roots [63].

ØTinospora cordifolia: it has been extensively studied and shown to have significant immune stimulating and antistress properties. *Tinospora cordifolia* is an important ingredient in a revitalizing recipe recommended in Ayurvedic literature to improve memory function. However, there is experimental evidence that *Tinospora cordifolia* has memory-enhancing properties [64].

ØMucunapruriens: *mucuna Pruriens* is also known as Atmagupta and is known as the Cowage Plant in English. In Ayurveda, *Mucuna Pruriens* has been recognized as a useful therapeutic agent for a variety of diseases of the reproductive and neurological systems. *Mucuna* beans are used in an Ayurvedic compound called Masabaladfi pacana which is effective in Kampavata. In 1937, Indian researchers Damodaran and Ramaswamy discovered L-dopa from *Mucuna* seeds. In HPLC experiments, the L-dopa concentration in whole *Mucuna* seeds was found to be 4.02 % [65-67].

ØCentellaasiatica: *Centella asiatica* is a plant native to Asia. It is known as Indian pennywort or Mandooki. Asiaticosid, brahmoside, brahminosides and thankuniside are triterpenoid saponine glycosides found in the drug. The hydrolysis of the asiaticoside produces two molecules of glucose, a rhamnose and the aglycone Asiatic acid. Alkaloids, sterols, tannins, amino acids and inorganic salts are also present in the drug. The plant has long been used to treat skin, nerve, and blood disorders. To improve memory, the leaves are consumed as a tonic.

ØGalanthusworonowii: *Galanthus woronowii* is a species of *Galanthus*. It's a snowdrop from the Caucasus. Galantamine is a pure, unadulterated *Galanthus* extract. According to a recent study, galantamine appears to slow the progression of neurodegenerative diseases. It also inhibits acetylcholine in a reversible and competitive manner. Galantamine reduces AChE synthesis while enhancing the brain's response to AChE. In one study, galantamine was found to reduce functional ability and cognition decline in 653 Alzheimer's patients with mild to moderate Alzheimer's disease [68, 69].

ØWithaniasomnifera: *Withania somnifera*, also known as Ashwagandha, is a Rasayana herb used in traditional Indian medicine. Although used primarily for medicinal purposes, the seeds and leaves are also used. Alkaloids and steroid lactones are the most pharmacologically active components. Cuscohygrain, tropane, anahygrain, somniferrin, anaferine, withanimine, and withaninine are the most common alkaloids, while withanoloids are the most common lactones. The root's total alkaloid content varies between 0.1 and 0.3 %, although larger yields may have been reported. According to Karnik (1991) Ashwagandha should be considered the most effective herb

for all age-related problems. There is evidence that the drug is effective in preventing senility and Alzheimer's disease. Alzheimer's disease causes progressive memory loss as well as deficiency in ability to function and care for self. The drug slows disease progression. Glycowithanolides (WSG) have also been discovered to repair both cognitive impairment and altered central cholinergic indicators caused by neurotoxic neurodegeneration, Bhattacharya, Ghosal, and Bhattacharya [72] discovered that ashwagandha normalizes SOD and LPO activity while enhancing CAT and GPx activity [70-72].

ØHemidesmus indicus: Hemidesmus indicus, sometimes known as Indian sarsaparilla or Anantmool, is a plant native to India. Its roots are believed to have antioxidant abilities, and experiments on mice have shown that it has nootropic (memory enhancing) potential. The n-butanol component of Hemidesmus indicus root extracts has been shown to improve memory.

ØTrapabispinosa: this floating herb is a medicinal plant that has been used as a nerve tonic since ancient times. It has been shown to be neuroprotective by reducing oxidative stress caused by D-galactose by activating glutathione peroxidase and catalase, thereby lowering lipid peroxidase [73, 74].

ØOcimum sanctum: scopolamine (0.4 mg/kg) and age-related memory deficits were both improved by an ethanolic extract of Ocimum sanctum. This improvement supported cholinergic modulation as a mechanism of action, implying potential value in the treatment of Alzheimer's disease and other age-related dementias [75].

ØClitoriaternatea: in India's Ayurvedic medicine, Clitoria ternatea is a well-known drug. Vyawahare, et al. studied the effect of alcoholic extracts of Clitoria ternatea roots on scopolamine-induced memory impairment using the radial arm maze and the condition avoidance response test [76].

ØAcorus calamus: several researches have looked at the neuroprotective benefits of a hydroalcoholic extract of Acorus calamus rhizomes against ischemia caused by middle cerebral artery occlusion (MCAO) and consequent neuronal damage. Cortical malonaldehyde decreases and glutathione and superoxide dismutase growth in the cortex and corpus striatum have been shown to be associated with significant improvements in rats [77].

ØPanax ginseng: another herb, panax ginseng, has been used for thousands of years to treat a variety of conditions, including age-related neurodegeneration. Animals given ginseng extract or combination therapies containing ginseng are believed to improve their learning and memory. Wang, et al. discovered that dosing reduced amyloid deposition or glutamate-induced excitotoxicity, resulting in neuronal death, which is a major cause of Alzheimer's disease [78, 79].
Coriandrum sativum: Coriandrum sativum is an herb that promotes blood flow to the brain, memory, and cognitive performance. It contains activities against free radicals and lipid peroxidation. An aqueous extract of coriander seed was discovered to protect pyramidal cells in the cerebral cortex against neurodegenerative diseases and Alzheimer's disease while increasing therapeutic effects.

Conclusion

Many people in impoverished countries use herbal medicines not only because they are considered harmless, but also because modern treatments are beyond the reach of many. Due to the increasing prevalence of severe metabolic and neurological diseases in Western societies without treatment, plant treatments could still be used as a vital source of lead compounds as they have throughout human history. A variety of plant species have produced biologically active secondary metabolites from polyphenols, particularly via the shikimic acid and/or acetate routes and other biosynthetic pathways, as well as other chemical groups such as alkaloids and terpenoids. Due to the abundance of data for neuroprotective chemicals of plant origin, there is a clear need for further exploration of the complexities of efficacy studies, particularly in humans. Secondary metabolites in medicinal and

food plants are a category of bioactive molecules that have the potential to benefit human health. Exposure to phytochemicals such as phenylpropanoids, isoprenoids, and alkaloids, found primarily in western industrialized countries, can promote health benefits through proper dietary habits, such as protection against chronic degenerative diseases such as cancer, cardiovascular disease, and neurodegenerative diseases.

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