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REVIEW

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Neuro-nutraceuticals: Insights of experimental evidences and molecular mechanism in neurodegenerative disorders

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Abstract

Background One of the most important healthcare challenges in the world today is neurological disorders. Pose lifestyle changes are linked to a significantly higher risk of chronic illnesses and diseases, placing a significant financial and healthcare burden on society at large. In this review article, we focused on the various neuro-nutraceutical herbs and their beneficial roles in neurodegenerative disorders.

Main body of the abstract An extensive literature review was done from the standard databases such as Scopus, Elsevier, and PubMed using standard keywords "Nutraceuticals", "Neuro-nutraceuticals", "Neurodegenerative disorders". Numerous "neuro-nutraceuticals" are natural plant compounds with dietary and pharmaceutical components that are intended to improve cerebral blood flow along with illness prevention and control. These compounds are found in food, herbal medicines, and nutritional supplements such *as Bacopa monnieri, Curcuma longa, Asparagus racemosus, Helicteres angustifolia, Hericium erinaceus, Crocus sativus, Uncaria tomentosa, Centella asiatica, Convolvulus pluricaulis, Moringa oleifera.*

Short conclusion While discussing the neuroprotective and the neuromodulatory properties of various neuro-nutraceuticals, we rationally postulate here their molecular mechanisms. Additionally, compared to single-target medicines, which may have unfavourable side effects, these herbs are believed to be safer and to provide a more holistic improvement in brain health.

Keywords Nutraceuticals, Neuro-nutraceuticals, Medicinal plants, A medicinal extract, Neuroprotective effect

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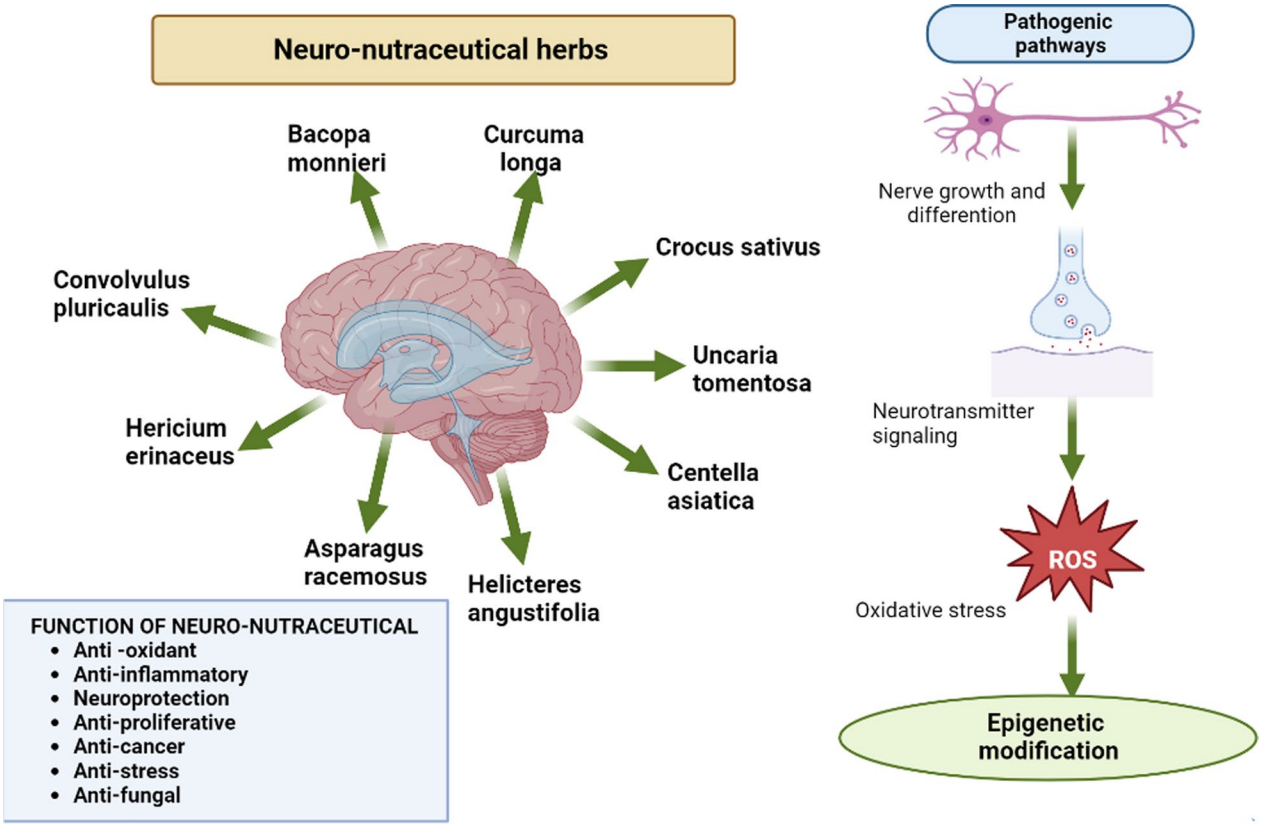
Graphical Abstract



Background

Nutraceuticals

Nutraceuticals, a type of supplement that has healing properties and may be used instead of conventional medication, have gained significant attention. In addition to food-prior medications, nutraceuticals may be a potent tool for treating and preventing clinical disorders, such as in patients who may not be candidates for standard medication treatment [1]. Nutraceuticals and nutritional supplements are phrases that are frequently heard indiscriminately and without any official meaning in the majority of nations. The world market for nutraceuticals, on the other hand, has grown a lot over the past few years [2].

A nutraceutical has been shown to provide physical advantages or to offer defence against degenerative illnesses [3]. Everyone uses nutritional supplements, but pregnant women, people with cancer, athletes, and people trying to lose weight are more likely to do so [4]. In light of this growing trend, every nutraceutical manufacturer attempts to introduce a new product to the market, to find things that have a clear purpose, and to suggest high-tech items that are good for your health [5].

People have started to look for a more assertive plan to improve health through meals or drugs that may provide additional health benefits than medications and a lower percentage of man-made substances. In response to this growing trend, each nutraceutical company tried to bring something new to the market in order to find products with specific functions and to suggest more complex products that would be good for health [6].

These are foods developed either by breeding of agricultural products and nutrients, such as orange juice fortified with calcium, fortified cereals. Since scientists successfully created methods to modify the nutritional content of crops, more research is being done to enhance the level of nutrition in crops [9]. These are the types of nutraceuticals developed through agricultural breeding to enhance nutrition, such as minerals in cereals, enhanced magnesium, folic acid, and iron in wheat, ergocalciferol fortify of milk to treat vitamin D insufficiency, etc. [7].

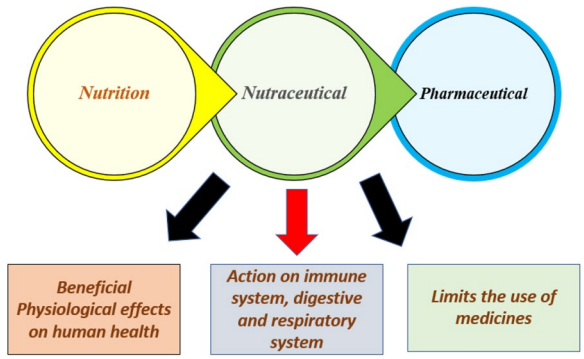


Fig. 1 Benefits of nutraceuticals

In order to distinguish their functions and assess their utilization, phytoconstituents have also been classified in antimicrobial, anti- fungal, antioxidants, anti-inflammatory, and anti-obesity categories depending on the therapeutic capabilities they exhibit. Food-borne infections are to blame for a large number of infection-related deaths. Quercetin (polyphenols), carbonic acid (terpenoids), and other bioactive substances have all been used as successful antibacterial treatments for infectious disorders. Numerous fruits and vegetables are the source of them [21, 35]. Various benefits of nutraceuticals are shown in Fig. 1.

Neuro-nutraceuticals

A vast range of natural plant substances known as "neuro-nutraceuticals" substances present in food, herbal remedies, and nutritional supplements have both dietary and pharmacological components designed to enhance blood flow to the brain as well as illness prevention and control [3]. The main cause of neurological diseases is protein misfolding (toxic conformations). Nutraceuticals primarily stop toxic conformations by preventing the production and stimulation of inflammatory cytokines. The mechanisms of neurogenesis are biologically programmable and very susceptible to external influences [7].

Among these influences, ideal nutrition stands out due to its substantial influence on the growth and development of the brain both during the time of pregnancy and beyond, but notably during the early years of life. Nutritional intake satisfies brain cells' needs for energy [8]. They influence signalling pathways, aid in neural architecture, and have derivatives.

The highest level of attention has been given to herbal supplements as a balanced blend of the bulk of the ingredients in neuro-nutraceuticals. Substances that are beneficial to the brain's health include flavonoids, saponins, omega-3 fats, B6 vitamins, ascorbic acid, and micronutrients like zinc, magnesium, and iron. Herbs are also thought to be safer and better for the brain's health in a wider range of ways than single-target drugs, which can have bad side effects [7, 9]. A diagrammatic representation of the extract of various herbs as nootropics is shown in Fig. 2.

Main text

Brain, cells, and biochemical contents

The brain is the body's most complicated organ. It has a variety of cell types that are identifiable by the expression of unusual proteins. By examining these proteins, we can determine a cell's phenotypic and degree of differentiation or functional state [10]. The brain's primary functional units, called neurons, are highly specialized excitable cells that interact with one another through specialized synaptic connections. Mature neurons can also be divided into glutamatergic, GABAergic, dopaminergic, serotonergic, and cholinergic categories based on their secretion. Any physiological changes in the brain may cause neurodegeneration and also affect the level of neurotransmitters and other biochemicals in the brain [11].

Oxidative stress is indicated by alteration in production and storage of DNA-damaging reactive oxygen species, which oxidize DNA, peptides, and lipids, commonly cause DNA mutations, and affect mitochondrial functions. When cells are immediately exposed to oxidative and deoxyribonucleic acid-damaging UV radiation, oxygen radicals and double-stranded DNA breaks are generated, which causes cells to undergo neoplastic transformation [12].

The signature characteristics and marker proteins of the brain cells are lost throughout this process. In addition to cancer, stress can accelerate aging and the onset of a number of cytodegenerative illnesses [10]. Thus, in Fig. 3, the schematic representation of the biochemical events are shown that are responsible to cause neurodegenerative disorders.

Potential neuro-nutraceuticals

The herb mentioned below is regarded as a good candidate for both the management and cure of neurodegenerative and mental illnesses as they function as potential neuro-nutraceuticals.

Bacopa monnieri

Herbal medicines make use of the popular medicinal plant *Bacopa monnieri (BM). Bacopa monnieri (L.),* a well-known ayurvedic medicinal herb used in India as a neural tonic to improve cognition, memory, and brain function as well as to lengthen the lifespan [13, 14], is a well-known nootropic herb and a member of the

Scrophulariaceae family. It improves brain activity and lifespan while acting as a brain tonic to improve cognition and learning [15]. The specific bioactive elements of BM that are responsible for its cognitive benefits are saponins called bacosides. The active ingredients in BM, bacosides A and B, are assumed to be the reason for the memory-improving benefits [16].

A phytochemical examination of BM preparations using high-performance liquid chromatography revealed that the main pharmacologically potent components are triterpene saponins of a dammarane type with aglycone valuable information jujubogenin or as a pseudo-jujubogenin motif (Bacopasides, Bacosides, and Bacopasaponins). The BM's capacity to enhance memory and cognition is significantly influenced by Levorotatory l (-) Bacoside A and dextrorotatory d (+) Bacoside [17, 18]. In Fig. 4, pharmacological mechanisms of bacosides are shown that are responsible to treat neurodegeneration and neurological disorders.

Experimental evidence and mechanism of action In the number of a preclinical studies in animal and in vitro model, along with epidemiologic studies on human cohorts, *Bacopa Monnieri* extracts and its biologically active constituents have been found to have favourable effects on the neurological (Alzheimer's-Disease, Parkinson's-Disease, Epilepsy) and mental (stress, melancholy, psychosis) impairments [19]. Bacosides A and B were definitely mentioned by Roshni et al. Monnieri serves as a strong substance that acts as a neuroprotectant to restore dopaminergic D1 receptor function and gene expression. Hypoglycemia affects Bax expression and changes it. Neonatal hypoglycemia promotes free radical buildup, which lowers SOD levels and leads to cortical cell death.

The pathological conditions of forgetfulness, dementia, and age-related mild dementia have all gained weighty endorsements for the *Bacopa Monnieri* extracts' abilities to support cognitive and other brain abilities. Oral treatment of bacosides-enriched extract like CDRI-08 (120 mg/kg body weight for seven days) indicated recovery of cognitive degradation in experimental mice in addition to improvement of learning and memory in healthy cohorts in the Scopolamine-induced amnesic Swiss albino mouse model [20, 21].

Knowing how active chemicals work paves the way for a physiological readout of specific molecular targets, such as enzymes or receptors, to which they bind. Some of the proposed mechanisms of action include a combination of antioxidant properties, calcium channel blocking action, pro cholinergic effects, GABAergic modulation, decrease of beta-amyloid, inhibition of neuronal oxidative, suppression of acetylcholinesterase, regulation of brain stress hormone, and/or anti-dopaminergic and anti-serotonergic properties.

Curcuma longa

The perennial Zingiberaceae plant *Curcuma longa*, often known as turmeric, is widely distributed across Southeast Asia, including Vietnam, China, and India. Furthermore, it is grown in neighbouring nations like Thailand, Malaysia, the Netherlands, Bangladesh, Burma and Indonesia. The underground stem (rhizomes) of this herb is a necessary ingredient in toothpaste, food, neighbouring, and spices. Turmeric is referred to as a "Ramayana" herb in conventional medical systems like Ayurveda and Unani. Turmeric has amazing nootropic effects in addition to anti-aging, anti-inflammatory, anti-diabetic, anticancer, anti-bacterial, and antioxidant properties [22]. Turmeric has incredible abilities to treat physiological abnormalities including obesity, ulcers, liver problems, and dysentery.

Experimental evidence and mechanisms of action Curcumin suppressed NF-κB signalling, reactive astrocytes and microglia, cytokine production (IL-23, IL-1, IL-6, and TNF), and PPAR- α transcriptional activity to diminish neuroinflammation [23–26]. In various experimental models of Alzheimer's disease, the antioxidant properties of curcumin—particularly its capacity to lower lipid peroxidation and scavenge ROS—helped to reverse oxidative stress [27].

Curcumin has shown both preventative and therapeutic effects in animal model trials against a variety of neurological diseases, including neuronal injury, brain tumours, convulsions, spinal injuries, sclerosis, and neuropathic pain [28, 29].

Asparagus racemosus

The word "asparagus" is derived from the Greek word for "shoot" or "stalk." The Asparagoideae subfamily and Asparagaceae family contain perennial herbaceous climbing plants known as asparagus species [30]. Alkaloids, flavonoids, carbohydrates, phenolic chemicals, and tannins were found in the hydroethanolic *A. racemosus* root extract during the phytochemical screening process, whereas steroids, terpenes, and saponins were found in the ethanolic extract [31]. The majority of the bioactive phytoconstituents found in asparagus species are steroidal saponins, which have a reputation for improving both male and female reproductive health in preclinical [32] and clinical contexts [33]. These compounds are similar to phytoestrogen. *A. racemosus* is a well-known nervine tonic in the Ayurvedic medicinal system and has a range of neurological effects, according to a study of the literature. *A. racemosus* is a well-known nervine tonic in the

Ayurvedic medicinal system and has a range of neurological effects, according to a study of the literature. Additionally, there were no fatalities reported in the oral acute toxicity testing using a dose of 3200 mg/kg of *A. racemosus* aqueous root extract [34].

Experimental evidence and mechanisms of action Iron deposition in certain brain regions, inflammatory processes with the growth of reactive microglia, and damage to the neuronal macromolecules from oxidation are some of the main pathogenic characteristics of ageing and neurodegenerative diseases like PD and AD [35]. This pushed scientists to investigate how *A. racemosus* guards against oxidative brain injury [36, 37]. The oxidative load in the hippocampus and striatal regions of mice was significantly reduced after prophylactic administration of a methanol extract, according to the studies. The pre-treated mice also had higher levels of glutathione peroxidase and GSH, two substances that scavenge the reactive oxygen species generated (ROS). *A. racemosus* may therefore have neuroprotective properties.

Plaques cause neurodegeneration and the hallmark clinical signs of dementia by accumulating in the intercellular space and interfering with inter-neuronal signalling. Oligomers accelerate the death of neurons by increasing their permeability to Ca2 + [38, 39]. In a new study, it was found that sarsasapogenin, a steroidal saponin from *A. racemosus*, might be able to stop the formation of amyloid [40, 41]. Because the oral acute and subchronic toxicity studies did not produce necropsy or any alterations in body weight at a high dose of 2000 mg/kg, the lethal dose (LD_{50}) of enzyme-treated asparagus extracts was reported to be higher than 2000 mg/kg [42].

Helicteres angustifolia

Small, grey-green, annual *Helicteres angustifolia* is also known as Chinese ginseng. It is typically seen on sloping grasslands in countries such as Australia, Thailand, Japan, Burma, Malaysia, and the Philippines, Syria, and the USA. *H. angustifolia's* roots, leaves, and other parts are being studied for potential medical uses, and its bark is a rich source of fibre.

Experimental evidences and mechanism of action Its roots have been demonstrated to have anti-diabetic properties. Its extract enhanced glucose absorption in these cells with an IC50 value of 79.95 g/mL in C2C12 myotubes and 135.96 g/mL in 3T3-L1 lipocytes, respectively. In Streptozotocin-induced diabetic rats, blood glucose, Homeostatic model assessment-IR (insulin resistance), TC, TG, UA, blood urea nitrogen, aspartate aminotransferase, and Alanine transaminase levels were significantly decreased after twenty-eight days of oral therapy with 200–400 mg/kg Body weight, while levels of TP and High-Density Lipoprotein cholesterol were increased. The different compounds in its shoot have been discovered to have antagonistic effects [43].

An isolated polysaccharide form DEAE called SPF3-1 significantly boosted macrophage proliferative rate, facilitated phagocytosis, and induced NO and immunomodulatory cytokines production. Water extracted from its roots exhibits significant antioxidant action [44].

It possessed stronger antioxidant and anticancer characteristics than its ethanolic equivalent, with a tumour inhibition rate of 49.83–14.38% in BALB/c nude mice. It showed considerable anticancer activity on DLD-1, A549, and HepG2 cell lines. By producing ROS and activating p53, its aqueous extract showed strong anticancer activity against the bone metastases U2OS cells. Strong anticancer activities can be found in terpenes that are isolated from the plant [45].

Hericium erinaceus

H. erinaceus is a traditional folk medicine that has gained popularity due to its anticancer, hepatoprotective, antibacterial, anti-inflammatory, antidiabetic, cardioprotective, and neurotrophic properties, in addition to having neuroprotective properties [46, 47]**.** According to both preclinical and clinical research [48–50], *H. erinaceus* helps with depression, anxiety, and trouble sleeping. It also improves brain function and protects neurons.

Experimental evidences and mechanism of action *H. erinaceus* significantly influences the Norepinephrine system's initiation and regulation of neurotrophins. *H. erinaceus* active ingredients, particularly the erinacines and hericenones, have potentive nerve growth factor stimulating properties and exhibit impressive nerve outgrowth functions in a variety of cell lines as well as dissociated neurons within the brain, vertebral column, and retina [51–53]. A daily, eight-week oral supplement with *H. erinaceus* (80% mycelium extract and 20% fruiting body extract), together with a low-calorie diet plan, has been shown to reduce sadness, stress, insomnia, and food addiction, according to a recent study on 77 subjects who were overweight or obese, eating, in contrast to participants on a reduced diet alone. Even though there were no noticeable changes in BDNF circulation, there was a link between this and the rising BDNF/BDNF ratio and pro-brain-derived neurotrophic factor levels in the circulation.

According to experiments using the elevated plus maze, tail suspension, and forced swimming, mice given

ethanolic fruit body extract from *H. erinaceus* at a dose of 60 mg/kg once a day for 4 weeks had less anxiety and severely depressed behaviour. According to studies using PCNA and Ki67 immunohistochemical in the sub granular zone of the hippocampus, this is associated with increased hippocampus precursor proliferation, faster neuron development, and BrdU/NeuN-positive cells in the hippocampus' dentate gyrus [54]. NGF-driven neurite development is accelerated by *H. erinaceus* because it activates the Trk/MEK/ERK and PI3K-Akt signalling pathways [55, 56]. In Fig. 5, brief neuroprotective mechanism of action of *Curcuma longa*, *Asparagus racemosus*, *Helicteres angustifolia* and *Hericium erinaceus* are shown.

Fig. 2 Benefits of various extracts of herbs as nootropics

Crocus sativus

Crocus sativus L. (C. sativus) is a perennial herb that is a member of the Iridaceae subfamily of the Liliaceae family. Saffron has a distinct colour, flavour, and aroma. It can be used as a fragrance as well as a spice for aroma and flavouring food dishes. It's interesting to know that saffron has long been used to cure memory problems in conventional Persian medicine. The main ingredients in *C. sativus*, crocin and safranal, have showed effects resembling those of antidepressants in animal models of depression [57].

Mechanisms of action and experimental evidence Bani et al. looked at how mice's humoral immunity levels of antibodies that recognize sheep erythrocytes were impacted by ethanolic extracts of saffron. When given at a dose of 5 mg/kg, cyclosporin significantly decreased the antibody titre response. The mouse agglutinating antibody titre was dramatically raised by *C. sativus* at a dose of 6.25 mg/kg, though. The levels of IgG-1 and IgM antibodies were also elevated by saffron in both primary and secondary immunological reactions [58].

The neuroprotective effects of safranal were investigated in a rat model of spinal cord injury. Safranal (25, 50, 100, and 200 mg/kg, three times daily) decreased IL-1β and TNF-α cytokine immunoreactivity and inflammatory expression after spinal cord injury and increased IL-10 expression after spine damage. At 100 mg/kg, safranal is primarily useful for spinal cord damage.

The mechanism(s) behind the beneficial cognitive effects of saffron and its bioactive component are still being studied. Some of the justifications given to explain their influence on cognition include the improvement of long-term potentiation, anti-amyloidogenic action, reduction of acetyl choline esterase activity, and potent antioxidant activities [59].

Uncaria tomentosa (cat's claw)

The Spanish word ua de gato is the source of the English name cat's claw, which describes the tiny, curved-back thorns on the stem near the leaf junction. Uncaria species, including South American species *U. guianensis* and *U. tomentosa*, have been identified. It is a common Rubiaceae family tropical therapeutic vine found throughout South and Central America, including the Amazon jungle [60, 61]. In the past, *U. tomentosa* was employed to treat viral infections, wounds, abscesses, fever, and other conditions.

U. tomentosa has purportedly been used in the past to treat viral infections, abscesses, fever and wounds [60]. It is also predicted to be beneficial as an immunostimulant, an antibacterial, an anti-inflammatory, and an antioxidant. *U. tomentosa* is the most useful supplementary plant for treating the majority of parasites [62].

It is significant to highlight approx 50 phytochemical compounds have been isolated from the *U. tomentosa* and identified, some of which are believed to be novel to the species [63]. In comparison to the stem bark etc. and branches, *U. tomentosa* leaves have a higher content of the oxindole alkaloid. This result agrees with earlier research by Laus et al. [64], which demonstrated that the principal oxindole alkaloids, speciophylline, and uncarine F, accumulate in leaves as either tetracyclic-oxindole-alkaloid (TOA) or pentacyclic-oxindole-alkaloid (POA)

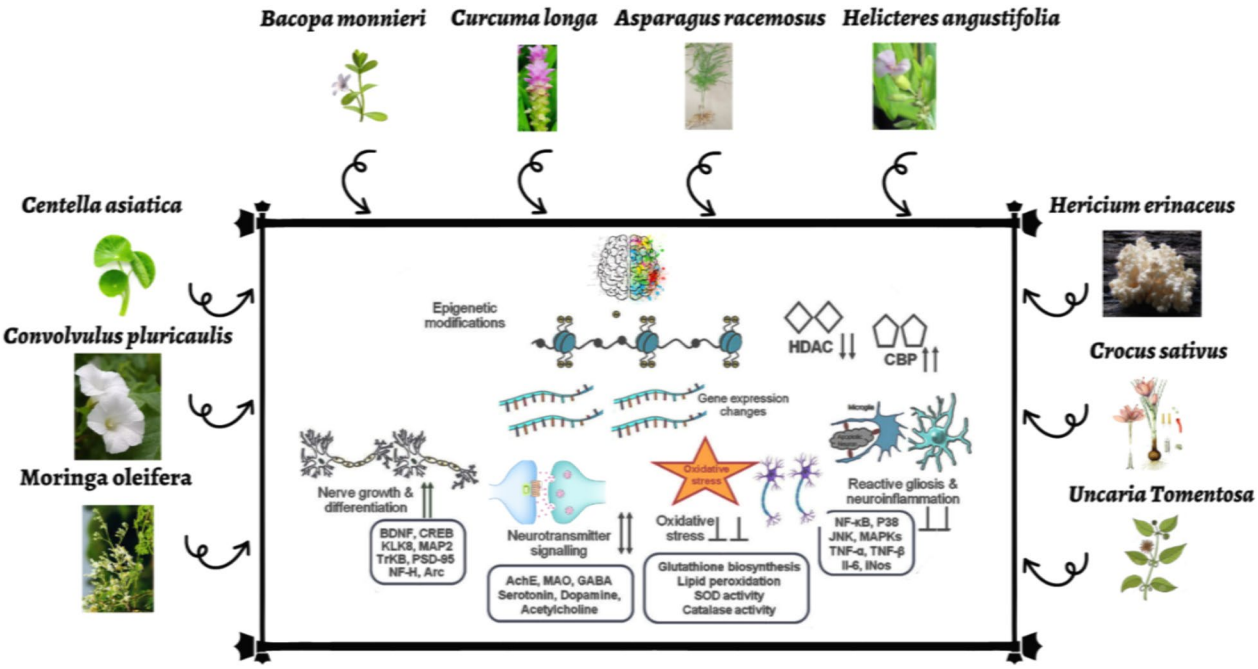


Fig. 3 Schematic representation of the biochemical events that cause neurodegenerative disorders

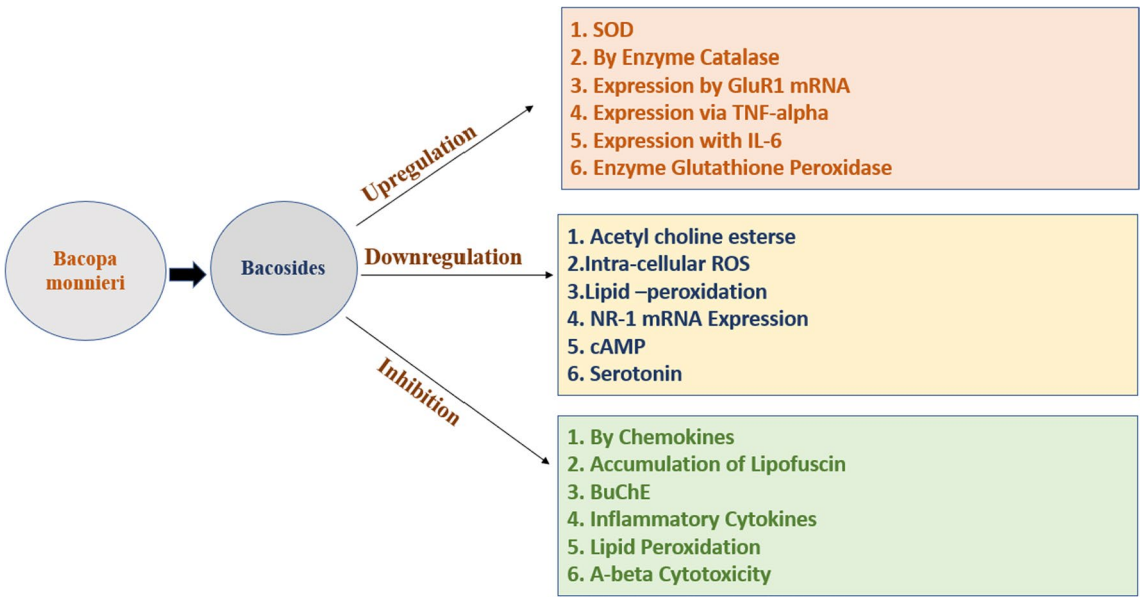


Fig. 4 Various pharmacological mechanisms of bacosides to treat neurodegeneration and neurological disorders

derivatives. Both TOA and POA are susceptible to isomerization, which is primarily influenced by the polarity, pH, and temperature of the medium [64].

Mechanisms of action and experimental evidence According to reports, *U. tomentosa* is a potential herb for Alzheimer's Disease (AD) therapies since it has a powerful medicinal extract that eliminates A plaques effectively. This occurred as a result of the presence of recently identified

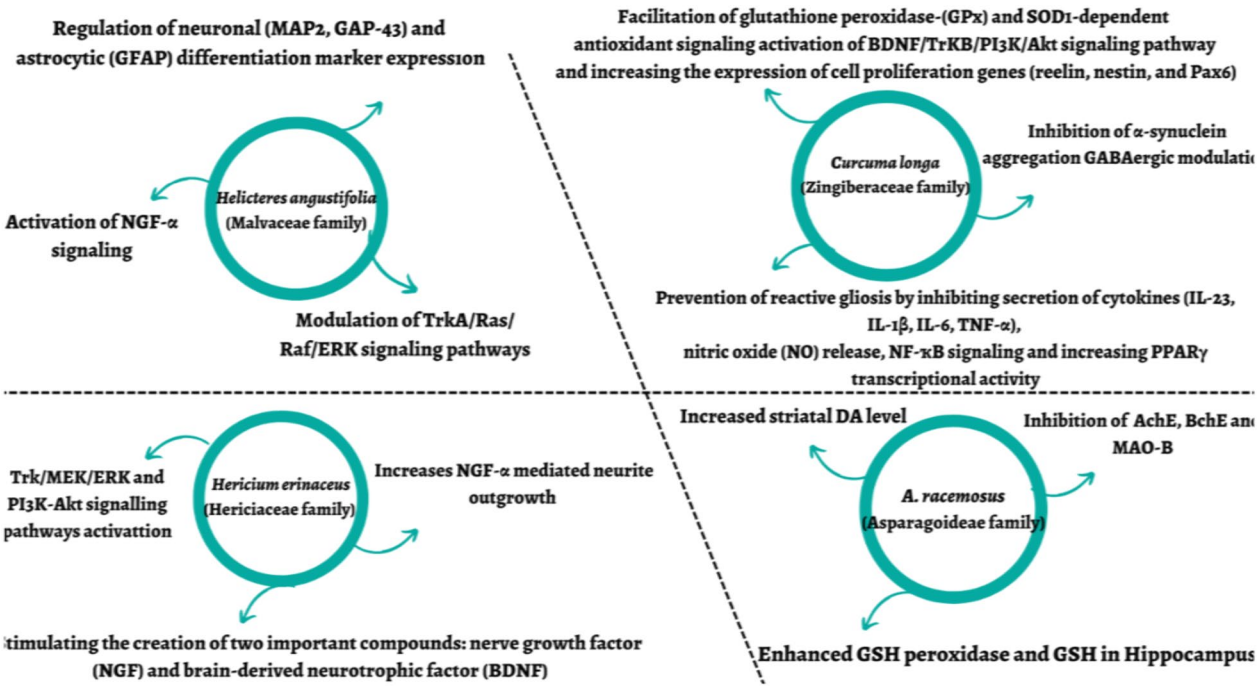


Fig. 5 Neuroprotective mechanism of action of the neuro-nutraceutical herbs

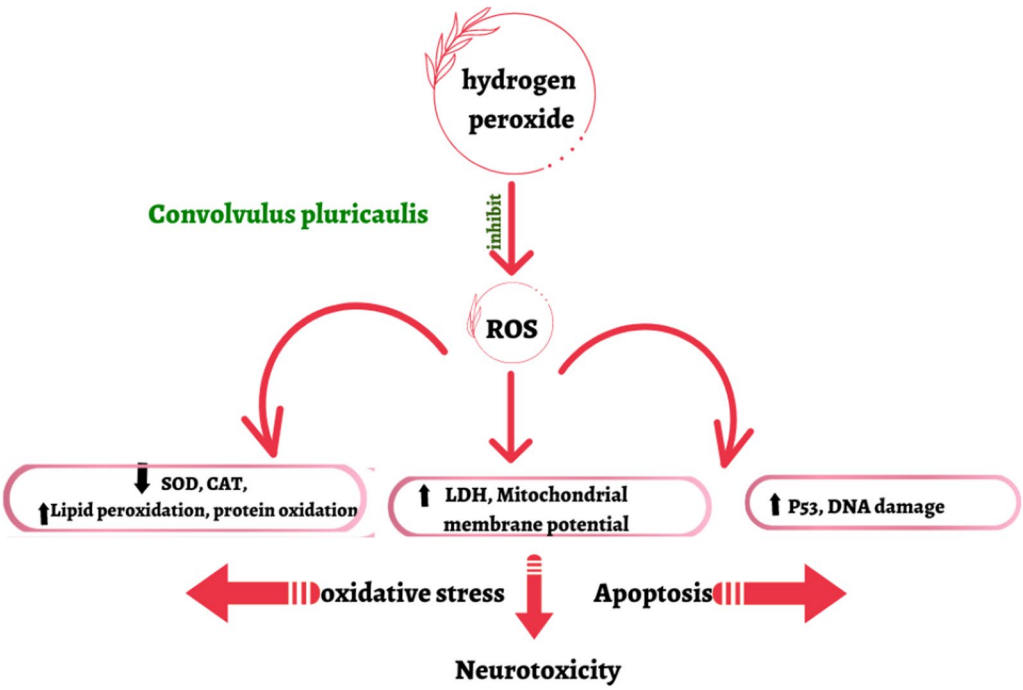


Fig. 6 Anti-oxidant and anti-apoptotic activity of *Convolvulus pluricaulis* against H_2O_2-induced neurotoxicity on SH-SY5Y human brain cells mediates its neuroprotective properties

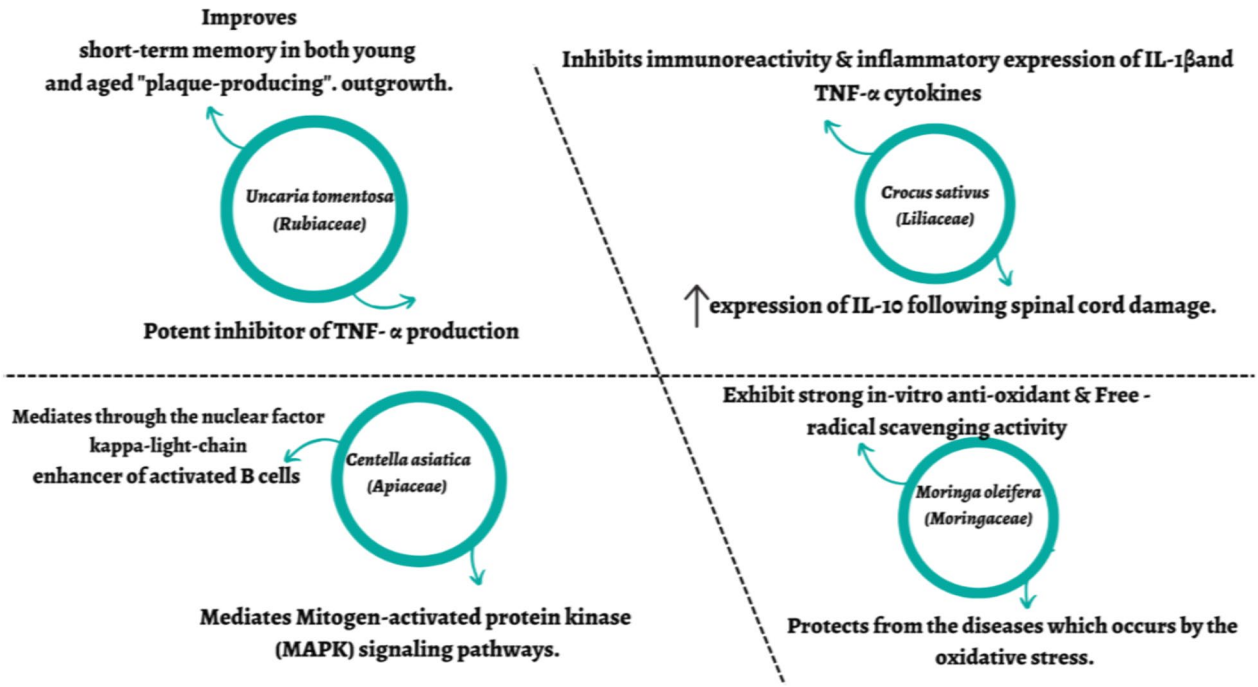


Fig. 7 Neuroprotective mechanism of action of neuro-nutraceutical herbs

polyphenolic chemicals in *U. tomentosa*, such as specific proanthocyanidins that inhibited growth and decreased "plaque and tangles."

In both young and old "plaque-producing" A precursor protein (APP) transgenic mice, the principal cat's claw-identified specific polyphenol proanthocyanidin B2 (epicatechin-4-8-epicatechin) dramatically decreased the brain plaque burden and enhanced short-term memory. Proanthocyanidin B2 is a powerful inhibitor of brain inflammation, as demonstrated by the decreased astrocytosis and gliosis in TASD-41 transgenic mice [65].

Large doses of cat's claw have been linked to a number of unfavourable side effects in past research, including diarrhoea, hepatotoxicity, vomiting, acute renal failure, decreased heartbeat, upset stomach, hormonal abnormalities, and neuropathy [66, 67]. Diagrams are used to display the cat's claw's additional pharmacological effects.

Centella asiatica (Gotu Kola)

Centella asiatica, well known as Gotu Kola (GK), is a creeping herb which grows widely throughout Asia, particularly in India. The Ayurvedic school of medicine uses the leaves of Gotu Kola as an alternate form of treatment for improving memory [68]. This leaf extract has been extensively researched for its potential medical benefits, including the enhancement of wound healing [69, 70], the reduction of inflammatory response and myofibroblast formation [71]. *Centella asiatica* L. (Gotu kola) has long been used to enhance memory, intelligence, and neurological protection. Memory is thought to be enhanced by *C. asiatica's* active pentacyclic-triterpenoid-saponins, including asiaticoside and madecassoside. Ramaswamy (2005) says that a drop in the modification of central monoamines, especially the 5-hydrotetraamine system (5-HT) and norepinephrine [72], is likely to improve memory.

Experimental evidence and mechanisms of action Triterpenoids from *C. asiatica* may affect neurological disorders by activating the phosphatidylinositol 3-kinase/protein kinase B/mTOR, nuclear factor kappa of activated B cells (NF-kB), and mitogen-activated protein kinase (MAPK) signalling pathways. The MAPK signalling pathway is activated by a variety of external stimuli, including growth factors, mitogens, hormones, cytokines, and different cellular stress factors. Numerous other AD-related processes, including tau phosphorylation, neurotoxicity, neuroinflammation, and synaptic dysfunction, are similarly influenced by the p38MAPK signalling network [73].

The *C. asiatica* extract also has a beneficial effect on leukaemia, oral submucous fibrosis, migraines, and toxic side effects. Leukaemia is the primary disease affected by

elevated oxidative scavenger activity. Leukemic THP-1 cells' activity was decreased by 28.404% by *C. asiatica* ethanolic leaf extract (CLE), according to in vitro testing. Furthermore, IL-10 levels increased while IL-1b and IL-6 levels decreased, possibly lowering cytokine-induced tumour immunosuppressive activity, cancer development, and cachexia syndrome.

In the brains of migraine animal models, 5-hydroxytryptophan levels and hyperalgesia were found to be successfully reversed by *C. asiatica*. When compared to the positive control (sumatriptan, 42 mg/kg1), the oral treatment agent, a standardized *C. asiatica* extract based on asiaticoside (AS), was successful in suppressing nociception in rats [74].

Convolvulus pluricaulis (Shankhpushpi)

Convolvulus pluricaulis, commonly known as Shankhpushpi, is utilized to enhance cognition and regenerate nerves [75–78]. *Convolvulus pluricaulis* belongs to the family Convolvulaceae. Triterpenes, flavonoids, proanthocyanidins, and steroids are the main chemical components and are what give Cp its neuro-enhancing and memory-improving effects [79, 80]. Numerous pharmacological effects of *Convolvulus pluricaulis* have been documented, including enhancement of memory and learning in both young and old mice [81] and neurologically enhanced remembrance, specifically for younger people who have long-term memory problems [81]. Additionally, CP is advised for mental exhaustion, anxiety, and sleeplessness. *C. pluricaulis* leaves have also been used to treat depression as well as other psychological issues [82, 83].

Experimental evidence and mechanisms of action Doses of 100 and 200 mg/kg, p.o., ethanolic extract of the *C. pluricaulis*, as well as its ethyl acetate and the aqueous fraction, demonstrated memory-enhancing properties [84]. Convolvine, a pharmacological component of *C. pluricaulis*, enhanced the memory-improving effects of choline and reduced cognitive impairment in AD [78, 85]. *C. pluricaulis* treatment for three months at a dose of 160 mg/kg prevented neurotoxic effects by lowering acetylcholine esterase activity, lowering damage from free radicals, and keeping ChAT and NGF-TrkA working [86].

In vitro, the synthesis of amyloid beta was inhibited in vitro by an alcohol extract of *C. pluricaulis* Choisy (leaves) [87]. The herb hasn't been assessed clinically despite thorough experimental investigations. *Convolvulus pluricaulis* substantially raised the MAP2 level during cerebral I/R injury and effectively decreased brain haemorrhage and oxidative stress [87]. In Fig. 6, the antioxidant and anti-apoptotic activity of *Convolvulus pluricaulis* is shown.

Moringa oleifera

The most widely dispersed species in Moringaceae family is *Moringa oleifera* (M. oleifera). The trees of this plant, which is indigenous to India, can grow up to 10 m tall. It has leaves that are bipinnate or tripinnate and brittle branches. *M. oleifera* oil is used for lubricating machinery, as biodiesel, and as an edible oil because of its excellent stability and abundant oleic acid content [88].

Experimental evidence and mechanisms of action Pretreatment with *Moringa oleifera* for an oral dosage of 200 mg/kg reduced the hypoxia-induced cognitive problems in rats via maintaining the concentrations of monoamine neurotransmitters in the brain [89]. A fourteen-day oral administration of the extract of ethanolic leaves at a dose of 250 mg/kg prevented the cognitive decline brought on by ICV-colchicine. It corrected the norepinephrine, serotonin, and dopamine alterations brought on by colchicine [90]. It reversed the effects of colchicine on dopamine, serotonin, and noradrenaline levels in the brain [91]. The neuroprotective activity action of *Crocus sativus*, *Uncaria tomentosa*, *Centella asiatica,* and *Moringa Oleifera* is shown in Fig. 7.

In rat models of AD caused by hyperhomocysteinemia, oleifera has been shown to attenuate hyperphosphorylation and Amyloid beta pathology [92]. Its aqueous extract of leaves was shown to be safe after being administered orally to rats at a dose of 2000 mg/kg, with LD_{50}values at 15.9 g/kg and 17.8 g/kg, respectively. Its acute toxicity of *M. oleifera* roots extracts both in water and in alcohol was examined in mice [92]. In Table No. 1, the active phytochemical constituents and their mechanism of action of herbs are elaborated. The marketed formulations of various herbs are mentioned in Table No. 2.

Conclusion and future perspective

Nature has given us excellent herbal substances that have a great deal of promise for the treatment and avoidance of serious illnesses and disorders linked to unhealthy lifestyles, such as neurodegeneration.

The neuroprotective, antiinflammatory, antioxidant, hypolipidemic, and healing qualities of nutraceuticals are responsible for their therapeutic effects. Through the suppression of antioxidants, a changing lifestyle has weakened the body's defence against free oxygen radicals, leading to an overflow of oxidative stress.

Age-related declines in antioxidant levels also seem to make people more susceptible to chronic illnesses.

Therefore, for years, the focus has been placed on targeting a variety of nutraceuticals for their therapeutic properties. Products containing antioxidants, such as vitamins, intrinsically act by scavenging free radicals and stimulating the synthesis of antioxidants in the body.

Table 1 Herbs active phytochemical constituents and their mechanism of action

S No	Herb	Family	Active phytochemical constituents	Proposed mechanism of action	References
1	*Bacopa monnieri*	Scrophulariaceae	Bacosides A, B	Synaptic plasticity gene expression regulation, chromatin modifying enzyme (DNMT, HDAC, and CBP), and modification of cholinergic, glutamatergic, and GABAergic neurotransmission are also involved	[16, 20, 21]
2	*Curcuma longa*	Zingiberaceae	Diferuloylmethane, Demethoxycurcumin, Bisdemethoxycurcumin	The expression of genes linked to cell proliferation is enhanced, and the BDNF/TrKB/PI3K/Akt signalling is activated	[24–26]
3	*Asparagus racemosus*	Asparagoideae	Shatavarin I-IV	Increased striatal DA level, Enhanced GSH peroxidase, and GSH in Hippocampus and Histritun, inhibition of Ache, BchE, and MAO-B	[36, 37]
4	*Helicteres angustifolia*	Malvaceae	*Flavonoids:* kaempferol 3-*O*-β-d-glucopyranoside, 5,8-dihydroxy-7,4′-dimethoxyflavone, takakin 8-*O*-β-d-glucuronide 6″-methyl ester and takakin 8-*O*-β-d-glucuronide 2″-sodium sulphate *Lignans:* lariciresinol, lirioresinol-B and (+)-pinoresinol	Modulation of TrkA/Ras/Raf/ERK signalling pathways, Activation of NGF signalling, Control of Neuronal (MAP2, GAP43), and Astroglial cell (GFAP) Differentiate Marker Expression, and NGF Signalilng Regulation	[44, 45]
5	*Hericium erinaceus*	Hericiaceae	Erinacines, Hericenones	By triggering the Trk/MEK/ERK and PI3K-Akt signalling pathways, H. erinaceus promotes NGF-mediated neurite outgrowth	[55, 56]
6	*Crocus sativus*	Liliaceae	Crocin and Safranal	It inhibits immunoreactivity and inflammatory expression of-IL-1β and TNF-αcytokines as well as higher expression of the Interleukin-10 following spine damage	[59]
7	*Uncaria tomentosa*	Rubiaceae	Proanthocyanidins, proanthocyanidin B2, and proanthocyanidin C1	It lessens the load of brain plaques and enhances short-term memory both in young and old "plaque-producing" individuals	[65]
8	*Centella asiatica*	Apiaceae	Triterpenoids glycosides asiaticoside and asiaticoside A	The nuclear factor of activated B cells (Nuclear factor), phosphatidylinositol 3 kinase/protein kinase B/mTOR, and mitogen-activated protein kinase (MAPK) signalling pathways may be involved in how C. asiatica triterpenoids affect neurological disorders	[73]
9	*Convolvulus pluricaulis*	Convolvulaceae	Triterpenes, flavonoids, Proanthocyanidins and steroids	Convolvulus pluricaulis substantially raised the MAP2 level during cerebral I/R injury and effectively decreased brain haemorrhage and oxidative stress	[87]
10	*Moringa oleifera*	Moringaceae	Scopoletin, β-sitosterol, cetyl alcohols, 20-oxodotriacontanol, tetratriacontanoic acids, flavonoid-kaempferol, steroids-phytosterols	The leaves and roots of M. oleifera plant exhibit potent in-vitro antioxidant and radical scavenging activity when extracted with water and alcohol (methanolic and ethanolic). Its leaves are abundant in antioxidant chemicals and may shield animals from ailments brought on by oxidative stress	[96,97]

Table 2 Marketed formulations of the given herbs

S.No	Herbs	Marketed formulations and brand name	Manufacturer
1	*Bacopa monnieri*	Brahmi Ghrita, Baidyanath Junior Chyawanprash Jain Memovit Flavoured Brahmi Granules Shree Guruji Brahma Tej Pitambari'sGeni Health and Memory Enhancer Granules Panchwati Health Prash Ayursona Fine Foods memory milk biscuits Basic Ayurveda Muslified Energic Drink Dabur Chyawanprash	Atrey Pharmaceuticals Shree BaidyanathAyurved Bhawan Pvt. Ltd Jain Ayurvedic Guruji Products Pvt. Ltd Pitambari products Pvt Ltd PanchwatiPrayogshala (P) Ltd Ayursona Fine Food Basic Ayurveda Dabur Ltd
2	*Curcuma longa*	Turmeric Liquid extract, Curcumin with Piperine (95%) veg capsules Complete Turmeric Matrix	Veda Oils BestSource Nutrition Palak Notes
3	*Asparagus racemosus*	Just Jaivik 100% Organic Shatavari Powder, USDA Organic, Asparagus Racemosus	HNCO Organics Private limited
5	*Hericium erinaceus*	Rooted Active Naturals	HerbalVeda Pharmacy
6	*Crocus sativus*	High Potency Saffron Extract Capsules 30 mg	Kiwla
7	*Uncaria tomentosa*	Dr Brahm's	Dr Brahm's
8	*Centella asiatica*	HealthyHey Nutrition	Healthy Hey Foods LLP
9	*Convolvulus pluricaulis*	Bliss Welness	Bliss Lifesciences LLP
10	*Moringa oleifera*	Ved Tattva	IshaAgro Developers Pvt Ltd

The current review highlights the experimental evidences and mechanism of action of neuro-nutraceutical, though nutraceuticals have been shown to exhibit remarkable properties, the response varies from person to person. They are the finest solutions for treating lifestyle-related mental problems because consuming them in acceptable and advised dosages promotes good neurological health and wards off diseases. These therapeutic plants have a wide range of phytochemicals that have been shown to enhance cognition, intelligence, attention, and concentration by preserving the proper level of the neurotransmitter acetylcholine inside the brain and by promoting a controlled function of the acetylcholinesterase enzyme (AChE). This review also indicates the efficient applications of the herbs described, which have improved cognitive and neuroprotective qualities, as well as their phytoconstituents, which can be utilized in the discovery of novel drugs.

Abbreviations

MAP2	Microtubule-associated protein 2
NF-KB	Nuclear factor kappa B
Akt-CREB	CAMP-response element binding protein
HDAC	Histone deacetylases
CBP	CREB-binding protein
TrkB	Tyrosine protein kinase
DNMT	DNA methyl transferases
PI_3K	Phosphoinositide 3-kinase
Akt	Ak strain transforming
GSH	Glutathione
Ache	Acetyl choline esterase
BchE	Butyrylcholinesterase
MAO	Mono amino oxidase
NGF	Nerve growth factor
GAP_{43}	Growth-associated protein 43
GFAP	Glial fibrillary acidic protein
RaS	Renin angiotensin system
Raf	Rapidly accelerated fibrosarcoma
ERK	Extracellular signal-regulated kinase
Trk	Tropomyosin receptor kinase
TrkA	Tropomyosin receptor kinase A
MEK	Mitogen-activated kinase
ERK	Extracellular signal-regulated kinase
MAPK	Mitogen-activated protein kinase
BDNF	Brain derived neurotrophic factor
mTOR	Mammalian target of rapamycin

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Availability of data and materials
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Declarations

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Consent for publication
The authors declare no conflict of interest.

Competing interests
The authors declare that they have no competing interests.

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References

1. Schilter B, Andersson C, Anton R, Constable A, Kleiner J, O'Brien J et al (2003) Guidance for the safety assessment of botanicals and botanical preparations for use in food and food supplements. Food Chem Toxicol 41(12):1625–1649
2. Cook G, Robbins PT, Pieri E (2006) "Words of mass destruction": British newspaper coverage of the genetically modified food debate, expert and non-expert reactions. Public Underst Sci 15(1):5–29
3. Nasri H, Baradaran A, Shirzad H, Rafieian-Kopaei M (2014) New concepts in nutraceuticals as an alternative for pharmaceuticals. Int J Prev Med 5(12):1487
4. Alsanad SM, Howard RL, Williamson EM (2016) An assessment of the impact of herb-drug combinations used by cancer patients. BMC Compl Altern Med 16(1):1–9
5. Siedlok F, Smart P, Gupta A (2010) Convergence and reorientation via open innovation: the emergence of nutraceuticals. Technol Anal Strat Manag 22(5):571–592
6. Bröring S (2010) Innovation strategies for functional foods and supplements. Challenges of the positioning between foods and drugs. Food Sci Technol 7(8):111–123
7. Stefani M, Rigacci S (2013) Protein folding and aggregation into amyloid: the interference by natural phenolic compounds. Int J Mol Sci 14(6):12411–12457
8. Georgieff MK, Ramel SE, Cusick SE (2018) Nutritional influences on brain development. Acta Paediatr 107(8):1310–1321
9. Makkar R, Behl T, Bungau S, Zengin G, Mehta V, Kumar A, Uddin M et al (2020) Nutraceuticals in neurological disorders. Int J Mol Sci 21(12):4424
10. Childs BG, Durik M, Baker DJ, Van Deursen JM (2015) Cellular senescence in aging and age-related disease: from mechanisms to therapy. Nat Med 21(12):1424–1435
11. Gomez-Mendoza M, Banyasz A, Douki T, Markovitsi D, Ravanat JL (2016) Direct oxidative damage of naked DNA generated upon absorption of UV radiation by nucleobases. J Phys Chem Lett 7(19):3945–3948
12. Gatz SA, Wiesmüller L (2008) Take a break—resveratrol in action on DNA. Carcinogenesis 29(2):321–332
13. Sõukand R, Pieroni A, Biró M, Dénes A, Dogan Y, Hajdari A et al (2015) An ethnobotanical perspective on traditional fermented plant foods and beverages in Eastern Europe. J Ethnopharmacol 170:284–296
14. Le XT, Pham HT, Do PT, Fujiwara H, Tanaka K, Li F et al (2013) Bacopa monnieri ameliorates memory deficits in olfactory bulbectomized mice: possible involvement of glutamatergic and cholinergic systems. Neurochem Res 38(10):2201–2215
15. Nannepaga JS, Korivi M, Tirumanyam M, Bommavaram M, Kuo CH (2014) Neuroprotective effects of bacopa monniera whole-plant extract against aluminum-induced hippocampus damage in rats: evidence from electron microscopic images. Chin J Physiol 57(5):279–285
16. Sukumaran NP, Amalraj A, Gopi S (2019) Neuropharmacological and cognitive effects of *Bacopa monnieri* (L.) Wettst–a review on its mechanistic aspects. Complement Ther Med 44:68–82
17. Sekhar VC, Viswanathan G, Baby S (2019) Insights into the molecular aspects of neuroprotective bacoside A and bacopaside I. Curr Neuropharmacol 17(5):438–446
18. Ramasamy S, Chin SP, Sukumaran SD, Buckle MJ, Kiew LV, Chung LY (2015) In silico and in vitro analysis of bacoside A aglycones and its derivatives as the constituents responsible for the cognitive effects of Bacopa monnieri. PLoS ONE 10(5):e0126565
19. Aguiar S, Borowski T (2013) Neuropharmacological review of the nootropic herb Bacopa monnieri. Rejuvenation Res 16(4):313–326
20. Downey LA, Kean J, Nemeh F, Lau A, Poll A, Gregory R (2013) An acute, double-blind, placebo-controlled crossover study of 320 mg and 640 mg doses of a special extract of Bacopa monnieri (CDRI 08) on sustained cognitive performance. Phytother Res 27(9):1407–1413
21. Konar A, Gautam A, Thakur MK (2015) *Bacopa monniera* (CDRI-08) upregulates the expression of neuronal and glial plasticity markers in the brain of scopolamine induced amnesic mice. Evidence-Based Compl Altern Med 2015:1–9. https://doi.org/10.1155/2015/837012
22. Hosseini A, Hosseinzadeh H (2018) Antidotal or protective effects of Curcuma longa (turmeric) and its active ingredient, curcumin, against natural and chemical toxicities: a review. Biomed Pharmacother 99:411–421
23. Lee WH, Loo CY, Bebawy M, Luk F, Mason RS, Rohanizadeh R (2013) Curcumin and its derivatives: their application in neuropharmacology and neuroscience in the 21st century. Curr Neuropharmacol 11(4):338–378
24. Begum AN, Jones MR, Lim GP, Morihara T, Kim P, Heath DD (2008) Curcumin structure-function, bioavailability, and efficacy in models of neuroinflammation and Alzheimer's disease. J Pharmacol Exp Ther 326(1):196–208
25. Koronyo-Hamaoui M, Koronyo Y, Ljubimov AV, Miller CA, Ko MK, Black KL (2011) Identification of amyloid plaques in retinas from Alzheimer's patients and noninvasive in vivo optical imaging of retinal plaques in a mouse model. Neuroimage 54(1):S204-217
26. Yanagisawa D, Amatsubo T, Morikawa S, Taguchi H, Urushitani M, Shirai N et al (2011) In vivo detection of amyloid β deposition using 19F magnetic resonance imaging with a 19F-containing curcumin derivative in a mouse model of Alzheimer's disease. Neuroscience 184:120–127
27. Sadegh Malvajerd S, Izadi Z, Azadi A, Kurd M, Derakhshankhah H, Sharifzadeh M (2019) Neuroprotective potential of curcumin-loaded nanostructured lipid carrier in an animal model of Alzheimer's disease: behavioral and biochemical evidence. J Alzheimers Dis 69(3):671–686
28. Luthra PM, Lal N (2016) Prospective of curcumin, a pleiotropic signalling molecule from Curcuma longa in the treatment of Glioblastoma. Eur J Med Chem 109:23–35
29. Sordillo PP, Helson L (2015) Curcumin suppression of cytokine release and cytokine storm. A potential therapy for patients with Ebola and other severe viral infections. In Vivo 1:1–4
30. Hazra K, Mandal AK, Mondal DN, Ravte RK, Hazra J, Rao MM (2019) Seasonal dynamics of Shatavarin-IV, a potential biomarker of Asparagus racemosus by HPTLC: possible validation of the ancient Ayurvedic text. Indian J Tradit Knowl 19(1):174–181
31. Venkatesan N, Thiyagarajan V, Narayanan S, Arul A, Raja S, Kumar SV (2005) Anti-diarrhoeal potential of Asparagus racemosus wild root extracts in laboratory animals. J Pharm Pharm Sci 8(1):39–46
32. Gupta M, Shaw B (2011) A double-blind randomized clinical trial for evaluation of galactogogue activity of asparagus racemosus Willd. Iran J Pharm Res IJPR 10(1):167
33. Thakur S, Sharma S, Thakur S, Rai R (2018) Green synthesis of copper nano-particles using Asparagus adscendensroxb root and leaf extract and their antimicrobial activities. Int J Curr Microbiol Appl Sci 7(4):683–694
34. Kumar MS, Udupa AL, Sammodavardhana K, Ratnakar UP, Shvetha U, Kodancha GP (2010) Acute toxicity and diuretic studies of the roots of Asparagus racemosus Willd in rats. West Indies Med J 59(1):3–5
35. Mandel S, Youdim MB (2004) Catechin polyphenols: neurodegeneration and neuroprotection in neurodegenerative diseases. Free Radical Biol Med 37(3):304–317
36. Geetanjali SR (2016) Asparagus racemosus: a review on its phytochemical and therapeutic potential. Nat Prod Res 30(17):1896–1908

37. O'brien RJ, Wong PC (2011) Amyloid precursor protein processing and Alzheimer's disease. Annu Rev Neurosci 34:185–204
38. Lee Y-J, Han SB, Nam S-Y, Ki-Wan Oh, Hong JT (2010) Inflammation and Alzheimer's disease. Arch Pharmacal Res 33(10):1539–1556
39. Rhein V, Baysang G, Rao S, Meier F, Bonert A, Müller-Spahn F, Eckert A (2009) Amyloid-beta leads to impaired cellular respiration, energy production and mitochondrial electron chain complex activities in human neuroblastoma cells. Cell Mol Neurobiol 29(6–7):1063–1071. https://doi.org/10.1007/s10571-009-9398-y
40. Kashyap P, Muthusamy K, Niranjan M, Trikha S, Kumar S (2020) Sarsasapogenin: a steroidal saponin from Asparagus racemosus as multi target directed ligand in Alzheimer's disease. Steroids 153:108529
41. Uddin M, Al Mamun A, Kabir M, Jakaria M, Mathew B, Barreto GE et al (2019) Nootropic and anti-Alzheimer's actions of medicinal plants: molecular insight into therapeutic potential to alleviate Alzheimer's neuropathology. Mol Neurobiol 56(7):4925–4944
42. Ito T, Ono T, Sato A, Goto K, Miura T, Wakame K (2014) Toxicological assessment of enzyme-treated asparagus extract in rat acute and subchronic oral toxicity studies and genotoxicity tests. Regul Toxicol Pharmacol 68(2):240–249
43. Yin X, Lu Y, Cheng ZH, Chen DF (2016) Anti-complementary components of *Helicteres angustifolia*. Molecules 21(11):1506
44. Li K, Lei Z, Hu X, Sun S, Li S, Zhang Z (2015) In vitro and in vivo bioactivities of aqueous and ethanol extracts from *Helicteres angustifolia L*. root. J Ethnopharmacol 172:61–69
45. Su D, Gao YQ, Dai WB, Hu Y, Wu YF, Mei QX (2017) Helicteric acid, oleanic acid, and betulinic acid, three triterpenes from *Helicteres angustifolia L*., inhibit proliferation and induce apoptosis in HT-29 colorectal cancer cells via suppressing NF-κB and STAT3 Signaling. Evidence-Based Compl Alternat Med. https://doi.org/10.1155/2017/5180707
46. Friedman M (2015) Chemistry, nutrition, and health-promoting properties of *Hericium erinaceus* (Lion's Mane) mushroom fruiting bodies and mycelia and their bioactive compounds. J Agric Food Chem 63(32):7108–7123
47. Liang B, Guo Z, Xie F, Zhao A (2013) Antihyperglycemic and antihyperlipidemic activities of aqueous extract of Hericium erinaceus in experimental diabetic rats. BMC Complement Altern Med 13(1):1–7
48. He X, Wang X, Fang J, Chang Y, Ning N, Guo H et al (2017) Structures, biological activities, and industrial applications of the polysaccharides from Hericium erinaceus (Lion's Mane) mushroom: a review. Int J Biol Macromol 97:228–237
49. Mori K, Inatomi S, Ouchi K, Azumi Y, Tuchida T (2009) Improving effects of the mushroom Yamabushitake (*Hericium erinaceus*) on mild cognitive impairment: a double-blind placebo-controlled clinical trial. Phytother Res 23(3):367–372
50. Chong PS, Fung ML, Wong KH, Lim LW (2019) Therapeutic potential of Hericium erinaceus for depressive disorder. Int J Mol Sci 21(1):163
51. Li I, Lee LY, Tzeng TT, Chen WP, Chen YP, Shiao YJ, et al (2018) Neurohealth properties of *Hericium erinaceus* mycelia enriched with erinacines. Behavioural Neurology
52. Kawagishi H, Ando M, Sakamoto H, Yoshida S, Ojima F, Ishiguro Y et al (1991) Hericenones C, D and E, stimulators of nerve growth factor (NGF)-synthesis, from the mushroom Hericium erinaceum. Tetrahedron Lett 32(35):4561–4564
53. Samberkar S, Gandhi S, Naidu M, Wong KH, Raman J, Sabaratnam V (2015) Lion's Mane, *Hericium erinaceus* and Tiger Milk, *Lignosus rhinocerotis* (Higher Basidiomycetes) medicinal mushrooms stimulate neurite outgrowth in dissociated cells of brain, spinal cord, and retina: an in vitro study. Int J Med Mushrooms 17:11
54. Ryu S, Kim HG, Kim JY, Kim SY, Cho KO (2018) Hericium erinaceus extract reduces anxiety and depressive behaviors by promoting hippocampal neurogenesis in the adult mouse brain. J Med Food 21(2):174–180
55. Zhang CC, Cao CY, Kubo M, Harada K, Yan XT, Fukuyama Y et al (2017) Chemical constituents from Hericium erinaceus promote neuronal survival and potentiate neurite outgrowth via the TrkA/Erk1/2 pathway. Int J Mol Sci 18(8):16–59
56. Phan CW, Lee GS, Hong SL, Wong YT, Brkljača R, Urban S (2014) Hericium erinaceus (Bull: Fr) Pers. cultivated under tropical conditions: isolation of hericenones and demonstration of NGF-mediated neurite outgrowth in PC12 cells via MEK/ERK and PI3K-Akt signaling pathways. Food Funct 5(12):3160–3169
57. Hosseinzadeh H, Karimi GH, Niapoor M (2004) Antidepressant effects of Crocus sativus stigma extracts and its constituents, crocin and safranal, in mice. J Med Plants 3(11):48–58
58. Bani S, Pandey A, Agnihotri VK, Pathania V, Singh B (2010) Selective Th2 upregulation by Crocus sativus: a neutraceutical spice. Evidence-Based Complement Altern Med 13:2011
59. Zhang C, Ma J, Fan L, Zou Y, Dang X, Wang K et al (2015) Neuroprotective effects of safranal in a rat model of traumatic injury to the spinal cord by anti-apoptotic, anti-inflammatory and edema-attenuating. Tissue Cell 47(3):291–300
60. World Health Organization (1999) WHO monographs on selected medicinal plants. World Health Organization
61. Heitzman ME, Neto CC, Winiarz E, Vaisberg AJ, Hammond GB (2005) Ethnobotany, phytochemistry and pharmacology of Uncaria (Rubiaceae). Phytochemistry 66(1):5–29
62. Santos KF, Gutierres JM, Pillat MM, Rissi VB, dos Santos Araújo MD, Bertol G et al (2016) Uncaria tomentosa extract alters the catabolism of adenine nucleotides and expression of ecto-5′-nucleotidase/CD73 and P2X7 and A1 receptors in the MDA-MB-231 cell line. J Ethnopharmacol 194:108–116
63. Navarro Hoyos M, Sánchez-Patán F, Murillo Masis R, Martín-Álvarez PJ, Zamora Ramirez W, Monagas MJ et al (2015) Phenolic assesment of *Uncaria tomentosa L*. (Cat's Claw): leaves, stem, bark and wood extracts. Molecules 20(12):22703–22717
64. Laus G, Brössner D, Keplinger K (1997) Alkaloids of peruvian Uncaria tomentosa. Phytochemistry 45(4):855–860
65. Snow AD, Castillo GM, Nguyen BP, Choi PY, Cummings JA, Cam J (2019) The Amazon rain forest plant *Uncaria tomentosa* (cat's claw) and its specific proanthocyanidin constituents are potent inhibitors and reducers of both brain plaques and tangles. Sci Rep 9(1):1–28
66. Cosentino C, Torres L (2008) Reversible worsening of Parkinson disease motor symptoms after oral intake of *Uncaria tomentosa* (cat's claw). Clin Neuropharmacol 31(5):293–294
67. Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, Grant L (2014) Liver injury from herbals and dietary supplements in the US drug-induced liver injury network. Hepatology 60(4):1399–1408
68. Mohandas Rao KG, Muddanna Rao S, Gurumadhva Rao S (2006) *Centella asiatica* (L.) leaf extract treatment during the growth spurt period enhances hippocampal CA3 neuronal dendritic arborization in rats. Evidence-Based Complement Alternat Med. 3(3):349–357
69. Biswas TK, Mukherjee B (2003) Plant medicines of Indian origin for wound healing activity: a review. Int J Low Extrem Wounds 2(1):25–39
70. Cheng CL, Koo MW (2000) Effects of Centella asiatica on ethanol induced gastric mucosal lesions in rats. Life Sci 67(21):2647–2653
71. Widgerow AD, Chait LA, Stals R, Stals PJ (2000) New innovations in scar management. Aesthetic Plast Surg 24(3):227–234
72. Ramaswamy G, Xu Q, Huang Y, Weisgraber KH (2005) Effect of domain interaction on apolipoprotein E levels in mouse brain. J Neurosci 25(46):10658–10663
73. Lee JK, Kim NJ (2017) Recent advances in the inhibition of p38 MAPK as a potential strategy for the treatment of Alzheimer's disease. Molecules 22(8):12–87
74. Bobade V, Bodhankar SL, Aswar U, Vishwaraman M, Thakurdesai P (2015) Prophylactic effects of asiaticoside-based standardized extract of *Centella asiatica* (L.) Urban leaves on experimental migraine: Involvement of 5HT1A/1B receptors. Chin J Natl Med 13(4):274–282
75. Malik J, Karan M, Vasisht K (2011) Nootropic, anxiolytic and CNS-depressant studies on different plant sources of shankhpushpi. Pharm Biol 49(12):1234–1242
76. Balkrishna A, Thakur P, Varshney A (2020) Phytochemical profile, pharmacological attributes and medicinal properties of convolvulus prostratus–a cognitive enhancer herb for the management of neurodegenerative etiologies. Front Pharmacol 11(3):1–71
77. Parihar MS, Hemnani T (2003) Phenolic antioxidants attenuate hippocampal neuronal cell damage against kainic acid induced excitotoxicity. J Biosci 28(1):121–128
78. Bihaqi SW, Sharma M, Singh AP, Tiwari M (2009) Neuroprotective role of Convolvulus pluricaulis on aluminium induced neurotoxicity in rat brain. J Ethnopharmacol 124(3):409–415

79. Mukherjee PK, Kumar V, Kumar NS, Heinrich M (2008) The Ayurvedic medicine Clitoria ternateafrom traditional use to scientific assessment. J Ethnopharmacol 120(3):291–301
80. Sethiya NK, Nahata A, Mishra SH, Dixit VK (2009) An update on Shankhpushpi, a cognition-boosting Ayurvedic medicine. Zhong Xi Yi Jie He Xue Bao 7(11):1001–1022
81. Sharma K, Bhatnagar M, Kulkarni SK. Effect of convolvulus pluricaulis choisy and Asparagus racemosus. Willd on learning and memory in young and old mice: a comparative evaluation
82. Singh VK, Ali ZA, Zaidi SH, Siddiqui MK (1996) Ethnomedicinal uses of plants from Gonda district forests of Uttar Pradesh, India. Fitoterapia 67(2):129–139
83. Nahata A, Patil UK, Dixit VK (2008) Effect of Convolvulus pluricaulis Choisy. on learning behaviour and memory enhancement activity in rodents. Natl Produc Res 22(16):1472–1482
84. Asthana S, Greig NH, Holloway HW, Raffaele KC, Berardi A, Schapiro MB (1996) Clinical pharmacokinetics of arecoline in subjects with Alzheimer's disease. Clin Pharmacol Ther 60(3):276–282
85. Mirzaev YR, Aripova SF (1998) Neuro-and psychopharmacological investigation of the alkaloids convolvine and atropine. Chem Nat Compd 34(1):56–58
86. Liu LF, Durairajan SS, Lu JH, Koo I, Li M (2012) In vitro screening on amyloid precursor protein modulation of plants used in Ayurvedic and traditional Chinese medicine for memory improvement. J Ethnopharmacol 141(2):754–760
87. Abd Rani NZ, Husain K, Kumolosasi E (2018) Moringa genus: a review of phytochemistry and pharmacology. Front Pharmacol 9:108
88. Ganguly R, Guha D (2006) Protective role of an Indian herb, Moringa oleifera in memory impairment by high altitude hypoxic exposure: possible role of monoamines. Biog Amines 20(3–4):121–133
89. Ganguly R, Guha D (2008) Alteration of brain monoamines & EEG wave pattern in rat model of Alzheimer's disease & protection by Moringa oleifera. Indian J Med Res 128:6
90. Mahaman YA, Huang F, Wu M, Wang Y, Wei Z, Bao J (2018) Moringa oleifera alleviates homocysteine-induced Alzheimer's disease-like pathology and cognitive impairments. J Alzheimers Dis 63(3):1141–1159
91. Adedapo AA, Mogbojuri OM, Emikpe BO (2009) Safety evaluations of the aqueous extract of the leaves of Moringa oleifera in rats. J Med Plants Res 3(8):586–591
92. Kasolo JN, Bimenya GS, Ojok L, Ogwal-Okeng J. Phytochemicals and acute toxicity of Moringa oleifera roots in mice

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