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Herbal Medicine as Neuroprotective Potential Agent in Human and Animal Models: A Historical Overview

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ABSTRACT

Neurodegenerative disorders could be a most important health issue within the 21st century. In the recent past; there has been a growing interest in medicinal plants. Chemical fruits and vegetables are said to decrease the possibility of many chief ailments, together with cardiovascular and cancer disorders as well as neurodegenerative ailments. Hence, who eat more fruits and vegetables may be less threaten for developing certain diseases caused by neurological dysfunction. The present review provides an overview of the about 14 most important plants used for neurological disorders and explores their neurological protection for the development of new pharmacological potential drugs. The data sources including the publications on Google Scholar, PubMed, and Science Direct. Publications searched with no particular time restriction in order to get a holistic and comprehensive view of the research done on this topic so far. Therefore, we present a systematic approach for herbal medicine as neuroprotective agent. From ancient time the herbal medicines are used to cure neurological symptoms. While the exact pharmacology of these herbs has not yet been set on, some of them have anti-inflammatory or antioxidant properties on different peripheral systems. The significant variety of medicinal plants makes it an essential source of healthy compounds compared to current therapeutic agents. In this review, the importance of phytochemicals for the function of neurological protection and other related disorders, in particular, the process mechanism and therapeutic prospective will be emphasize.

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Introduction

In the recent past, there has been a growing interest in medicinal plants where phytochemical components can promote health or achieve long-term benefits for drugs. In turn, several medicinal herbs take particular drugs without having a nutritional character in the human nourishment and can be used to respond to particular health harms during short or long-term periods. Chemical fruits and vegetables are said to decrease the threat of many chief ailments, as well as cardiovascular, cancer and neurodegenerative ailments. Hence, who eat more vegetables and fruits may be less risk of developing certain diseases caused by neurological dysfunction (1, 2).

From ancient time the herbal medicines are used to cure neurological symptoms. While the exact pharmacology of these herbs has not yet been set on, some of them have anti-inflammatory or antioxidant properties on different peripheral systems. As more indication recommends that chronic

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inflammatory reactions in the nervous system perform a pathological character in the central nervous system, herbs and their chemical constituents act as a potent neuroprotective agent. The main important variety of medicinal plants makes it a chief source of healthy compounds compared to current therapeutic goals in the study of genomes and proteomics. In this review, the importance of phytochemicals for the function of neurological protection and other related disorders, in particular, the process mechanism and therapeutic prospective will be emphasize (3).

The most complicated structure of the human body can be described as the brain. It consists of neurons and neuroglia. The neuron is responsible for sending and receiving nerve signals (4). The neurons and neuroglia are fast to get involved when neurons become damaged or strained. As they are patrols of neuron well-being, pathological loss of microglia could have severe penalties for role of the brain. It is estimated that neuroglial activation usually concludes by neuronal signals (5).

Neuropathy is concerned with the mechanisms that are capable of protecting both acute (such as strokes or traumas) and chronic nervous system dysfunction like Parkinson's disease and Alzheimer's disease (6, 7). Furthermore, stroke and dementia cause high personal and family distress due to the deficiency of effective treatment options. In recent year's research accelerated hard work to recognize the new mechanisms of neurological death and determined the combinations to cure them. Nootropic is originated from the Greek words and means to practice the mind and it is use for smart medicine and food supplements that have a positive result on the brain role (8, 9). The "Green" movement in Western civilization has altered their approaches in the whole population who now consider as expected resulting ingredients and extracts as being characteristically harmless and extra essential than artificial chemical yields, with the net influence of rise in sales of herbal products (10). For the treatment of Central Nervous System (CNS) ailments, more than 120 herbal drugs are used in Asian countries (7). Some of the traditionally used plants having neuroprotective properties from the centuries are given below.

Methods

This study is a review study and the data sources including the publications on Google Scholar, PubMed, and Science Direct. Publications searched with no particular time restriction in order to get a holistic and comprehensive view of the research done on this topic so far with following terms: (Herbal medicine, Neurodegenerative disorders, Medicinal plants, Central Nervous System, Herbal medicine and food supplements, Anticonvulsant and anti-Alzheimer activity of plants, Antioxidative activity of plants, Peripheral neuropathy, Neuronal degenerative, Cerebral ischemia, Anti-inflammatory, antioxidant and immunoregulatory effects of plants).

Results

Study selection for this review was done in three steps: In the first step, titles of papers were searched according to the selected terms. Then, suitable titles were selected and enter the next step. At the second step abstracts of the papers were reviewed and eligible papers selected. At the end step full text of the eligible papers were evaluated. In total, 1,547 papers were evaluated, of which, 1,442 papers were excluded because of no consistency with the study goals. Also, 25 papers were deleted due to the type of language (Another language: like Turkish or Arabic) or no new important data. Finally, 80 papers were included in this review paper.

Crocus sativus

Saffron is a derivative of Crocus sativus L flowers in the form of dried stigma. It belongs to the Iridaceae family and Crocoideae super family. It is cultivated in numerous nations such as Spain, Afghanistan, Iran, and Turkey (11). Saffron consists of 150 altered constituents such as polypeptides, carbohydrates, lipids, H2O, vitamins and minerals. In saffron four chief active constituents are crocin, crocetin, picrocrocin and safranal (12). Crocus sativus is used to cure mental ailments in traditional Iranian system of medicine. Recently saffron ingredients are used to cure specific neural ailments and to relax smooth muscle (13, 14). It shows an anticonvulsant and anti-Alzheimer activity in humans and animal models (15). The C. sativus can treat the depression in experimental clinical education, and influence the brain neurotransmitter attention and interaction with the opioid system. Crocin is the most important constituent of C. sativus, which has antioxidant properties via decreasing of Malondialdehyde (MDA) level (16, 17). The intake of 100 mg/kg, p.o, C. sativus extract before initiation of cerebral ischemia by central cerebral artery obstruction expressively condensed glutamate and aspartate concentrations, SOD, catalase, and K-ATPase actions made by ischemia in mice (18). Furthermore, intake of C. sativus extract (200 mg/kg) and syrup of honey for 45 days decreased the aluminum chloride-induced neurotoxicity in rats (19).

Nigella sativa

Nigella sativa L. belongs to the family Ranunculaceae. It is a yearly herb and broadly cultivated in the Mediterranean nations, Eastern Europe, Middle East, and Western Asia. The N. sativa seeds are mixed as a flavor in different Persian diets like, pickle, bread, sauces, and salads (20). The Chemical constituents of N. sativa seeds are oil, carbohydrate, protein, fiber, oleic acid, linoleic acid, Palmitic acid, Arachidic acid, Eicosadienoic acid, Stearic acid, Linoleic acid and Myristic acid (21). The main phenolic complexes are 37.3% of p-cymene, 11.77% of carvacrol, 13.7% of Thymoquinone (TQ), and 0.33% of thymol (22, 23). N. sativa is a medicinal herb and used as antioxidative activity (24). In rats, N. sativa seeds also play an important role in spatial cognitive insufficiencies initiated by chronic cerebral hypo perfusion (25). Additionally, N. sativa enhanced scopolamine e encouraged learning and memory deficiency also decreased AChE action and oxidative stress of the mice's mind (26). N. sativa and thymoquinone (TQ) effects as neuroprotective on various nervous system disorders such as Alzheimer's

disease, epilepsy, and neurotoxicity have been studied in human and animal models (13).

Coriandrum sativum

Coriandrum sativum belongs to the Apiaceae family. It is a yearly grown plant. This plant is commonly named "Geshniz" in Persian, and Coriander is inborn to the Mediterranean area, and it is widely cultivated worldwide (27). The major constituents are fixed oil contains linalool and certain other oxygenated monoterpene and monoterpenes hydrocarbons (28). It also contains lipids like petroselinic acid and a high quantity of essential oils (EO), these essential oil play a significant role in development and brain roles. The chief coriander EO is linoleic, linalool, and linolenic acids (29). Coriander is extensively used as digestive representative in traditional system of medicine. The seed extract of C. sativum is also used in pharmaceutical products such as shampoos, lotions, applies antimicrobial, and anti-rheumatoid properties. C. sativum also recommended to treating insomnia in the Iranian system of traditional medicine (30). The aqueous extracts intake 0.5 g/kg, i.p. and ethanolic extracts intake 3.5 and 5 g/kg, i.p. from seeds of coriander has been used an experiment using pentylenetetrazole (PTZ), and the highest electroshock seizure models show anticonvulsant properties. These extracts reduced the period of stimulant seizures and presented a crucial, anticonvulsant action in the highest electroshock experiment in mice. Furthermore both extracts of coriander seeds, particularly ethanolic extract (5 g/kg, i.p.) parallel to phenobarbital (20 mg/kg) extended beginning latencies of colonic convulsions in mice (31).

Ferula asafoetida

Asafoetida (F. asafoetida L.) is a medicinal herb that has its place in the Apiaceae family, and its botanical name is Ferula asafoetida. It gained from the exudates of the existing rhizome of herbs. Asafoetida also called gum-resin is famous as "Anghouzeh", "Khorakoma", and "Anguzakoma" in the area of Iran (32). The main constituent is E-1-propyl sec-butyl, and there are 25 other constituents also recognized in the hydro distilled oil. E-1-propenyl sec-butyl disulfide (40.0%) and 7.8% of germacrene B (33). The scholars have been given importance to F. asafoetida (Apiaceae) because of its therapeutic and nutritious belongings. Roots, leaves and young shoots of herbs are used as cooking a meal. Ferula asafetida leaves have therapeutic properties like carminative, anthelmintic and diaphoretic and the root of this herb also has antipyretic activity (34). Furthermore, F. asafoetida is also had numerous ailments containing stomachache, asthma, flatulence, epilepsy, intestinal parasites, weak digestion and influenza in different traditional system of treatment (35).

Asafoetida also has expectorant, sedative, carminative, analgesic, stimulant, antiperiodic, ant-diabetic, antispasmodic, emmenagogue, vermifuge, laxative, anti-inflammatory, contraceptive and anti-epileptic activities (36). The researchers stated that oleo gum-resin of asafoetida could improve renewal and re-myelination and declines the rate of lymphocyte penetration in the neuropathic muscle in rats; thus, its action as a neuroprotective and nerve simulative agent in peripheral neuropathy (37). It is scientifically proved that it can also use in the treatment of neurodegenerative ailments like Parkinson's and Alzheimer's diseases (38). In the behavioral model, inactive prevention test, the lesser quantity of extract (200 mg) cannot increase memory while in high quantity (400mg), it improved memory in Wistar rats (39). Moreover, it also recognized that the extract of F. asafoetida showed anticonvulsant activity in Pentylenetetrazol (PTZ) and amygdala-kindled mice. Scientists examined the outcome of two quantities of F. asafoetida (50 and 100 mg/kg) on limits of seizure, and the results shown that a quantity of 100 mg/kg applies the enhanced anticonvulsant influence than 50 mg in mice (36).

Ocimum sanctum

Ocimum sanctum commonly known as tulsi is widely used in Ayurveda medicine and is having multitude neuromodulatory effect including the anticonvulsant effect in acute seizure models. Previous studies showed that, ethanol obtained from the leaves of Ocimum sanctum could stimulate and reestablish the appearance of choline acetyltransferase in endothelial cells of small cerebral blood vessels and provide nerve protection and nerve stimulation in the human body (40). Researchers have revealed that alcohol extract in the Ocimum sanctum shows an intense antioxidant activity against hydroxyl radicals and DPPH, which are because of flavonoids and polyphenols. It prevents lipid peroxidation, ROS generation, DNA damage, and membrane depolarization. It also reduces lactate dehydrogenase damage and maintains cell morphology, restores superoxide levels, and inhibits catalyzing enzymes in vitro (41).

Panax ginseng

Ginseng is from a growing family of Araliaceae in North-East Asia. It is one of the plants to enhance energy used extensively (42). Ginseng root is categorized by the occurrence of ginsenosides. It protects against neurodegeneration through a variety of mechanisms. Ginsenosides may increase neuroprotection. Genesis increase the presentation of passive prevention learning forms, and neuroprotection was probable, as it improved the skill to quash cellular AChE movement and increase cholinergic metabolic rate in animal models (43). It also produced a decrease in β-amyloid deposition or glutamate-induced excitotoxicity. Thus it inhibits apoptosis and neuronal loss. In various experimental models of Parkinson disease (PD), It quashes the production of nitric oxide and necrotic tissue elements alpha secretion (TNF, α), inducible nitric oxide synthase (iNOS), TNF-α, Interleukin (IL 1β). This inhibits the expression, will decrease cyclooxygenase-2 (LAME-2) and generation of ROS in vitro (44).

Glycyrrhiza glabra

Glycyrrhiza glabra (G. glabrous), commonly named as "Yashti-madhuh or liquorice", has a place to family Leguminosae. The main flavonoid of liquorice is Glabridin

that has numerous pharmacological properties like antiviral, anticancer, anti-ulcer, anti-diabetic, antioxidant, immunomodulatory action, antimicrobial movement, anti-inflammatory action, and anticonvulsant. Liquorice mainly progressed learning and memory, but the study has shown that its utilization moves forward the universal insights instead of short-term memory in male adolescents (45). Glabridin altogether reduces the level of MDA, and it raises the level superoxide dismutase and compact glutathione within the brain in rats (46). A considers demonstrated that intake of G. glabra reestablished the reduced levels of brain chemicals such as glutamate and dopamine and reduced AChE action in hypoxic rats (47).

Acorus calamus

Acorus calamus (Sweet flag) having, family Araceae, acts as a rejuvenator to improve the characteristics of the brain and nervous system; improve the performance and behavior of learning. Acoruscalamus has a main constituents of α-and β-asarone, the β-asarone are accomplished of reducing beta-amyloid-which produced neuronal apoptosis within the hippocampus by inversion down-regulation of Bcl-2, Bcl-w, caspase-3 actuation and c-Jun N-terminal kinase (JNK) phosphorylation in the beta-amyloid hippocampus injection rats (48). The Methanolic extract of Acoruscalamus roots has α-asarone which inhibitory properties on AChE by an IC50 value of 188μg/ml in vitro (49). Acoruscalamus has the capability of progressing the work of dopaminergic nerve; by expanding striatal extracellular dopamine level and the appearance of tyrosine hydroxylase in substantial, nigra hence, it acts in PD. Acoruscalamus, too increases DJ-1 gene expression within the striatum and thus acts as neuroprotective for PD in mice (50).

Allium sativum

Allium sativum belongs to family Amaryllidaceae, generally, identified as garlic, it is one of the leading medicinal herbs originate within the ancient medicinal research principally for its therapeutic possibilities in inhibition and treatment of cardiovascular and other metabolic illnesses, hyperlipidemia, atherosclerosis, thrombosis, dementia, hypertension, cancer and diabetes (51, 52). Allicin is the main constituents of Allium sativum. S-allyl cysteine (SAC) is the main component of matured garlic extract, which is broadly considered (53, 54). SAC has antioxidant properties. Separated from diminishing lipid peroxidation and DNA fracture, it too diminishes protein oxidation and nitration. In 1-methyl-4-phenyl pyridinium (MPP) and 6-hydroxydopamine (6-OHDA) models of Parkinsonism, SAC ensured dopamine levels, oxidative harm, and lipid peroxidation. In 3-nitro propionic corrosive and quinolinic corrosive animal models of HD, intake of SAC reduced lipid peroxidation and mitochondrial dysfunction. It also improved manganese and copper/zinc superoxide dismutase action and prohibited behavioral variations. AGE, openly and incidentally, starts the expression of significant genes desirable for neuronal survival in vitro (55, 56). Alliin also stimulates transient receptor probable ion channels in the plasma membrane of the nervous system in human and animal models (57).

Curcuma longa

Curcuma longa is a well-known medicinal plant from Zingiberaceae family and is planted within the Southeast Asian nations (58). The turmeric contain dynamic constituents are Curcumin flavonoid or diferuloylmethane and different unstable oils. The volatile oils consist of atlantone, tumerone, and zingiberone. Further compounds are sugars, resins and proteins. The main accomplished dynamic ingredient is curcumin (59). A few herbs such as Curcuma longa have a non-flavonoid and common polyphenol compound which are also known as curcumin. Curcumin is importantant and well-known because of its few impacts, like antioxidant, anti-inflammatory etc. Prvious studies showed that curcumin water solvable extract in mice has ability to elevate dopamine, nor-epinephrine and 5-HT levels in CNS (60). The defensive properties of C. longa extract (1000 mg/kg, body weight) on oxidative stress (61) and renal impairment has been described in rat kidney (62). In addition it has been described to intake of curcumin (50, 100, 200 mg/kg) enhanced mental shortages and mitochondrial dysfunctions indications in rats (63). Curcumin has been demonstrated as protect nervous system impacts, in neuronal degenerative clutters and in permanent focal cerebral ischemia in rats (64, 65). Scientific researches express that curcumin saves the mice brain in opposition to focal ischemia through up regulation transcription factor Nrf2 and HO-1expretion (66).

Ginkgo biloba

Ginkgo Biloba belongs to Ginkgoaceae family and it also called as kew tree, maiden hair tree, ginkyo, yinhsing and is native to East Asia. It has been prescribed in conventional medication of TCM for the purpose of decrease memory caused by variations in blood distribution (67). The medicinal plant improve the memory loss by increasing oxygen supply, in this way memory improved by removing free radicals. Ginkgo Biloba contain ingredients such as ginkgolides, terpenoids bilobolide, flavonoids, steroids and natural acids. Extract of Ginkgo Biloba leaves consists of 6% terpenic lactones and 24% flavonoids. The flavonoid distribution is mostly collected of three isorhamnetin, flavonols, keampferol and quercetin, though terpenic subordinates are spoken to by diterpenic lactones, a sesquiterpenic trilactone, the ginkgolides A, B, C, J and M, the bilobalide (67). Ginkgolides and Bilobalide display in Ginkgo biloba have been categorized as Nootropic agents in animal models (7).

Centella asiatica

Centella asiatica L. Urban belongs to family Apiaceae or Umbelliferae, and used as a psychoactive therapeutic plant being utilized from ancient time in Ayurvedic framework of pharmaceutical as a medhya rasayna (68). It has been appeared to reduce the oxidative stress symptoms. Highly active constituents of this plant consist of exceedingly changeable triterpenoid saponins, brahminoside,

oxyasiaticoside counting asiaticoside, centelloside, brahmoside, thankunoside, isothankunoside and sapogenins. In addition, it has triterpenoid acids viz. madecassic corrosive Asiatic corrosive, isobrahmic corrosive, brahmic corrosive, and betulic corrosive etc. It is able to affect the brain; indeed, it is employed for its cognitive properties as a brain tonic and for its ability to improve learning performance and memory in animal models (69).

Salvia officinalis

Salvia has long history utilized as memory enhancing plant which belongs to Lamiaceae family (70). The most dynamic constituents of S. officinalis are Rosmarinic corrosive and carnosic corrosive are having potential medicinal impacts that consist of anti-inflammatory, antioxidant activities and also have weak inhibitory impact on AChE (71, 72). It restrains oxygenation, lipid peroxidation, DNA fracture, caspase-3 enactment and tau protein hyperphosphorylation (73). In this way symptoms of dementia reduce by this clinical evidence. On little trial it appeared that oral intake of S. officinalis basic oil to 11 patients appearing mild-to-moderate symptoms of AD considerably enhance the function brain in human study (74).

Centella asiatica

Centella asiatica described as neuroprotective agent which belongs to family Apiaceae (Umbelliferae), from ancient time it is used as traditional medicine to enhance memory (75). The main ingredients of Centella asiatica are saponins, which contain asiaticosides, in which a trisaccharide moiety is associated to the madasiatic acid, aglyconeasiatic acid and madecassoside. Further constituent isolated which may be responsible for CNS action are brahmoside and brahminoside (76). Centella asiatica has antioxidant property, accomplished of removing free radical, decrease ferric ions, restores GSH levels by elevating the glutathione-S-transferase action. Centella asiatica also reduces Aβ accamulation in the CNS. The researchers described that the ethanolic exract of Centella asiatica could repressed Aβ-induced neurotoxicity by increasing the antioxidative defence system in differentiated PC12 and IMR32 cells in vitro (77, 78). Amelioration of the colchicine-induced reduces in AChE action and reserve of nitric oxide induced neuronal impairment by asiaticoside may also make clear the neuroprotective action of Centella asiatica in rats (79, 80).

Conclusion

In this review we evaluated the neuroprotective effects of herbal medicine in a variety of researches and found the action of the herbal medicinal on nervous system. The above detailed of therapeutic plants take part in their defensive actions by means of enhanced catalase levels SOD, reduced MDA levels, renovation of GSH and also secure of basic unit of nervous system in opposition to antioxidant actions. A few defensive properties of these plants origin constituents perhaps because of decrease Ca2+, Na+ and increase 'anti-glutamatergic' activity. The neural protective impacts of the said herbs happen through the improvement of anti-inflammatory cytokines and decrease of inflammatory cytokines, through alteration GABAergic and glutamatergic neurons, the acetyl cholinesterase action restrained and reduced MDA levels within the nervous system, so in neurotransmitter system the quantity of amino acids and serotonins increased. Moreover, on different ailments these herbs shows anti-inflammatory, antioxidant and immunoregulatory activity through the clinical evidences.

This discovery offer assistance to suggest the utilized of these plants and the most important constituents derived from natural source for medicine improvement and more examination within the clinical researches for future.

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