Neuroprotective potency of some spice herbs, a literature review

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1. Introduction

Neurodegenerative diseases such as Alzheimer’s Disease (AD), Parkinson’s disease, Multiple Sclerosis (MS) results in slow neuronal death that accompanied with losing cognitive functions and sensory dysfunction.1 Recently, these diseases associated with different multifactorial etiologies, social, and financial problems.2 Anti-inflammatory agents have also been suggested to postpone the progression of neurodegenerative diseases such as AD.3 Different studies have shown that nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of developing AD.4,5 Pathological processes including inflammation, oxidative stress, apoptosis, mitochondrial dysfunction, and genetic factors lead to neuronal degeneration in Parkinson’s disease (PD).6 It has been reported that excessive lipid peroxidation may destroy cholinergic neurons in AD7 and dopaminergic neurons in PD.8 Different enzymatic antioxidant such as superoxide dismutase (SOD)9 and non-enzymatic antioxidant such as total thiols10 exist in the brain. Central nervous system (CNS) also contains high level of polyunsaturated fatty acids is more sensitive to peroxidation reactions (9). Low antioxidant activity of the brain with respect to other tissues has been made the brain tissue susceptible to oxidative damage.11 In traditional medicine, the organs of plant such as: leaves, stems, roots, flowers, fruits and seeds were used as alternative and complementary therapy. Some derived components from herbs such as resveratrol, curcumin, ginsenoside, polyphenols, triptolide, etc. have neuroprotective effects.12 Herbal products contain of complex active components or phytochemicals like flavonoids, alkaloids and isoprenoids. Therefore, it is frequently difficult to determine which component(s) of the herb(s) has more biological activity.13,14

In the present review study, it was aimed to highlight the useful effects of different medicinal plant which used traditionally for neuro-inflammation and neurotransmitter deficiency such as AD and depression.

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dietary, food additive, spice and various medicinal purposes on induced neurotoxicity.

2. Methods

The information’s of this review were obtained from databases such as, PubMed, Web of Science, Google Scholar, Scopus, and IranMedex until the end of August 2016. The search terms were included “neuroprotective” or “neurotoxicity” and “Crocus sativus”, “Nigella sativa”, “Coriandrum sativum”, “Ferula assafoetida”, “Thymus vulgaris”, “Zataria multiflora”, and “Curcuma longa”. All studies such as, in vitro studies, animal studies, review articles and clinical studies with the outcome of changes in the neurotransmitter releasing, behavioural changes, oxidant/anti-oxidant parameters and pro-inflammatory cytokines were included. Letter to the Editor and Unpublished data were the exclusion criteria.

3. Neuroprotective effects of medicinal plants

3.1. Crocus sativus

Crocus sativus L. (C. sativus), commonly known as saffron belongs to the Iridaceas family, Crocoideae superfamily which is cultivated in many countries including Iran, Afghanistan, Turkey and Spain. Saffron consists dried and dark-red stigma with a small portion of the yellowish style attached of C. sativus. It used mainly as herbal medicine in various regions in the world. Saffron possesses 150 different compounds including carbohydrates, polyphenides, lipids, H2O, minerals and vitamins. Crocins are the main biologically active ingredients of saffron, a family of red-colored and water-soluble carotenoids, which are all glycosides of the main biologically active ingredients of saffron, a family of red-colored and water-soluble carotenoids, which are all glycosides of crocin, crocetin, picrocrocin and safranal. Another constituent of saffron was Picrocrocin which has a bitter taste.

3.1.1. Medicinal properties of C. sativus

In Iranian traditional medicine, Crocus sativus is used to treat cognitive disorders. Recently C. sativus constituents were used to treat some neural disorders and to relax smooth muscle. The anticonvulsant and anti-Alzheimer properties of saffron extract in (30 mg/day) for six-week was effective in the treatment of mild to moderate AD in the patients of 55 years and older was found to be as effective as donepezil and the frequency of saffron extract side effects was similar to those of donepezil except for vomiting. Similarly, the uses of saffron in 46 patients with mild-to-moderate AD for 16 weeks improved the cognitive functions. Saffron extract (30 mg/day) for six-week was effective in the treatment of mild to moderate depression similar to the effects of fluoxetine and imipramine (100 mg/day). In a double-blind clinical trial the efficacy of co-administration of hydro-alcoholic extract of C. sativus (40 and 80 mg) and fluoxetine (30 mg/day) for six weeks was investigated. The results showed that a dose of C. sativus 80 mg and fluoxetine (30 mg/day) was effective than that of C. sativus 40 mg to treat mild to moderate depressive disorders.

3.2. Nigella sativa

Nigella sativa L. (N. sativa) is an annual herbaceous and belonging to Ranunculaceae family, which widely grown in the Mediterranean countries, Western Asia, Middle East and Eastern Europe. The N. sativa seeds have been added as a spice to range of Persian foods such as, bread, pickle, sauces and salads. Chemical components of N. sativa seeds include oil, protein, carbohydrate, and fiber. The fixed oil chemical compositions of N. sativa are linoleic acid, oleic acid, Palmitic acid, Arachidic acid, Eicosadienoic acid, Stearic acid, Linoleic acid and Myristic acid. The major phenolic compounds of N. sativa seeds are p-cymene (37.3%), Thymoquinone (TQ) (13.7%), carvacrol (11.7%), and thymol (0.33%).

3.2.1. Medicinal properties of N. sativa

N. sativa as a medicinal plant is well-known for its potent anti-oxidative effects. It has been reported that N. sativa have protective effects on the renal damage. N. sativa seeds could significantly ameliorate the spatial cognitive deficits caused by chronic cerebral hypo perfusion in rats. Furthermore, N. sativa improved scopolamine – induced learning and memory impairment as well as reduced the AChE activity and oxidative stress of the rats brain. Antioxidant effects of N. sativa oil on the patients with rheumatoid arthritis (RA) showed N. Sativa reduced the serum level of IL-10, MDA and NO. N. sativa also improved inflammatory responses and reduced oxidative stress in patients with RA. In the other clinical trial, 40 healthy volunteers were divided into the treatment with capsules of N. sativa (500 mg) and placebo (500 mg) twice daily for 9 weeks. N. sativa enhanced memory, attention and cognition compared to the placebo group. N. sativa (500 mg) also decrease anxiety, to stabilize mood and to modulate cognition in the human model after 4 weeks. Neuroprotective effects of N. sativa and thymoquinone (TQ) (its major components) on various nervous system disorders such as Alzheimer disease, epilepsy and neurotoxicity have been reviewed.

3.3. Coriandrum sativum

Coriander (Coriandrum sativum L.), is an annual herb of the parsley family (Apiaceae). This plant is generally called Geshniz in Persian. Coriandrum sativum is native to the Mediterranean region and is extensively grown in all over the world. The aliphatic aldehydes (mainly C10-C16 aldehydes) with fetid-like aroma are predominant in the fresh herb oil whereas major components in the oil isolated from coriander fruit include linalool like aroma are predominant in the fresh herb oil whereas major components in the oil isolated from coriander fruit include linalool and some other oxygenated monoterpene and monoterpenic hydrocarbons. Coriander is also a potential source of lipids such as petroselinic acid and a high amount of essential oils (EO) that are very important for growth and brain functions. The main coriander EO is linalool, linoleic and linolenic acids. Coriander seed oil was contains linalool (60–70%) and 20% hydrocarbons but the composition of the herb oil was completely differs from the seed oil.

3.3.1. Medicinal properties of C. sativum

In folk medicine, coriandrum sativum (C. sativum) was widely used as digestive agent. The seed extract of C. sativum was used in lotions and shampoos and exerts antimicrobial and anti-inflammatory effects. In Iranian traditional medicine, C. sativum has been suggested to relieve insomnia. A combination of the fresh leaves extract and tea, or crushed of plant seeds as a single dose before sleeping have been suggested to relieve anxiety and
insomnia. Similar uses of *C. sativum* seed have been shown in other folk medicines. The leaves extract of *C. sativum* (200 mg/kg) showed an anxiolytic effect which was presented by increasing the time spent in open arms and the percentage of open arm entries. *C. sativum* fruit extract (100 and 200 mg/kg, i.p.) increased the time spent in the open arms and entries into the open arms. Locomotion activity and frequency of rearing also decreased in the groups treated by 200 mg/kg (i.p.) of the extract. Furthermore, *C. sativum* extract at 100 and 200 mg/kg increased the time spent in social interaction. Anticonvulsant activity of aqueous (0.5 g/kg, i.p.) and ethanolic extracts (3.5 and 5 g/kg, i.p.) of coriander seeds were studied using pentylenetetrazole (PTZ) and the maximal electroshock seizure models. These extracts decreased the duration of tonic seizures and showed a significant anticonvulsant activity in the maximal electroshock test. In addition both extracts especially ethanolic extract (5 g/kg, i.p.) similar to phenobarbital (20 mg/kg) prolonged onset latencies of clonic convulsions.

3.4. Ferula asafoetida

Asafoetida (*F. asafoetida* L) belongs to the Apiaceae family which obtained from the exudates of the living underground rhizome or tap root of the plant. *F. asafoetida* or gum-resin is known as “Anghouzeh”, “Khorakoma” and “Anguzakoma” in Iran. It has been used in traditional medicine and as a spice in different foods in India and Nepal. E-1-propyl sec-butyl disulfide is a major component and 25 compounds were identified in the hydrodistilled oil. E-1-propenyl sec-butyl disulfide (40.0%) and germacrene B (7.8%) are the major components of Ferula assa-foetida.

3.4.1. Medicinal properties of *F. asafoetida*

*F. asafoetida* (Apiaceae) is considered by researchers due to its medicinal and nutritional properties. Roots, young shoots and leaves of plant are eaten as vegetable. Leaves of Ferula asafoetida possess anthelmintic, carminative and diaphoretic properties and the root of plant is used as antipyretic. In addition, *F. asafoetida* is used for treatment of various diseases including asthma, epilepsy, stomachache, flatulence, intestinal parasites, weak digestion and influenza in traditional medicine. It has also been reported that oleo-gum resin of *F. asafoetida* possesses sedative, expectorant, analgesic, carminative, stimulant, antiperiodic, anti-diabetic, anti-spasmodic, emmenagogue, vermifuge, laxative, anti-inflammatory, contraceptive and anti-epileptic effects. Effects of *F. asafoetida* on muscarinic receptors and possible mechanisms for functional antagonistic of guinea-pig tracheal smooth muscle have been studied. The relaxant effect of *F. asafoetida* on smooth muscles and its possible mechanisms have been reviewed. Pharmacological and biological studies, the oleo-gum- resin of *Ferula asafoetida* have been revealed to have antioxidant, antiviral, antifungal, anti-diabetic, molluscidal, antispasmodic and anti-hypertensive effects. In a study, acute and sub-chronic toxicity of *F. asafoetida* was evaluated and the results indicated that single oral administration (500 mg/kg) and repeated doses (250 mg/kg) for 28 days of this plant did not induce mortality and obvious toxicological signs in rats. It has also been documented that oleo gum resin of *F. asafoetida* can enhance regeneration and re-myelination and decreases the rat of lymphocyte infiltration in the neuropathic tissue in mice; therefore it acts as a neuroprotective and nerve simulative agent in peripheral neuropathy. Scientific evidences have also shown that *F. asafoetida* resin can potentially inhibit monoamine oxidase B (MAO-B) and it can be used in the therapy of neurodegenerative diseases such as Parkinson’s and Alzheimer’s diseases. Meanwhile, *Ferula asafoetida* has been reported to have acetylcholinesterase (AChE) inhibiting property in vitro assay and in vivo on snail nervous system. Researchers have proposed that memory increasing effect of *Ferula asafoetida* could be attributed to inhibitory effect of this plant on AChE in the rat brain. In behavioural models, such as elevated plus maze, the extract of plant dose-dependently improved memory in rats. In another behavioural model, passive avoidance test, the lower dose of extract (200 mg) could not improve memory whereas in high dose (400 mg) it ameliorated memory. Additionally, it has been documented that the extract of *F. asafoetida* applies a considerable anticonvulsant effect in Pentylenetetrazol (PTZ) and amygdala-kindled rats. Researchers investigated the effect of two doses of ferula asafoetida (50 and 100 mg/kg) on parameters of seizure and the results revealed that dose 100 mg/kg exerts the better anticonvulsant effect than 50 mg.

3.5. Thymus vulgaris

*Thymus vulgaris* (*T. vulgaris*) is a plant that is a member of Lamiaceae family which are strongly aromatic. This plant is consist of approximately 38 species and is distributed in subtropical countries. The phenols, thymol (40%) and carvacrol (15%) are main components of TV. It contains less amounts of phenol during the winter. Also, thymol methyl ether (2%), cineol, cymene, pinene, borneol and esters are components in the essential oil.

3.5.1. Medicinal properties of *T. vulgaris*

*Thymus vulgaris* (Thyme) is a subshrub native to the western Mediterranean region which is widely used as spice to add a distinctive flavour to food. In the traditional medicine, thyme is part of herbal teas and infusions. It has been documented that bioactive compounds of thyme such as thyme essential oil (TEO) constituents, flavonoids and phenolic acids, natural terpenoid thymol and phenol isomer carvacrol, possess antioxidant, antimicrobial, antitussive, antiinflammatory, contraceptive and anti-epileptic effects. Effects of *F. asafoetida* on muscarinic receptors and possible mechanisms for functional antagonistic of guinea-pig tracheal smooth muscle have been studied. The relaxant effect of *F. asafoetida* on smooth muscles and its possible mechanisms have been reviewed. In pharmacological and biological studies, the oleo-gum- resin of *Ferula asafoetida* have been revealed to have antioxidant, antiviral, antifungal, anti-diabetic, molluscidal, antispasmodic and anti-hypertensive effects. In a study, acute and sub-chronic toxicity of *F. asafoetida* was evaluated and the results indicated that single oral administration (500 mg/kg) and repeated doses (250 mg/kg) for 28 days of this plant did not induce mortality and obvious toxicological signs in rats. It has also been documented that oleo gum resin of *F. asafoetida* can enhance regeneration and re-myelination and decreases the rat of lymphocyte infiltration in the neuropathic tissue in mice; therefore it acts as a neuroprotective and nerve simulative agent in peripheral neuropathy. Scientific evidences have also shown that *F. asafoetida* resin can potentially inhibit monoamine oxidase B (MAO-B) and it can be used in the therapy of neurodegenerative diseases such as Parkinson’s and Alzheimer’s diseases.

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shortened the immobility time in tail suspension tests (TST) and forced swimming test (FST) and restored the reduction of the hippocampal levels of serotonin (5-HT) and norepinephrine (NE) in chronic unpredictable mild stress (CUMS)-induced depressive mice.80

3.6. Zataria multiflora

_Zataria multiflora_ (Z. multiflora) is belonging to the Lamiaceae family.83

It have consist of p-cymene derivatives: multi-flotriol (1), multi-flrol (2), a new aromatic ester of p-hydroxy benzoic acid (3) and three known constituents: dihydroxyaromadendrane,84 luteolin85 and a-tocopherolquinone.86 The main components of the plant oil were thymol (37.59%), carvacrol (33.65%); PARA-cymene (7.72%), γ-terpinene (3.88%) and β-caryophyllene (2.06%).87

3.6.1. Medicinal properties of _Z. multiflora_

_Z. multiflora_ contains various compounds including terpen, luteolin, 6-hydroxyuteolin glycosides, di-, tri, and tetra-ethoxylated which could be responsible for the therapeutic effects of it.88 _Z. multiflora_ Boiss essential oil (ZEO) possesses preservative effects whereas vigorous taste and aroma have limited its usage as food preservative in high amounts.89 In Iranian traditional medicine, the plant is used for its analgesic, antiseptic and carminative effects.89 It has also been documented that the essential oil of _Z. multiflora_ has antioxidant, antibacterial and antifungal properties in _in vitro_.89,90 The results of studies have indicated that the ZEO exhibited more potent antioxidative effect than pomegranate juice.89 Antibacterial,90 immunoregulatory91,117 and anti-inflammatory92,118 effects of this plant have also been reported. In addition, it has been reported that the Aβ-caused learning and memory impairments could be restored by i.p. administration of _Z. multiflora_ essential oil in rats. Therefore zataria multiflora essential oil was considered to be as a worth source of natural therapeutic agent for attenuating cognitive symptoms of Alzheimer’s disease (AD) by researchers.93

3.7. _Curcuma longa_

_Curcuma longa_ (C. longa) is a member of the Zingiberaceae family and is cultivated in the countries of Southeast Asia.94

The active constituents of turmeric are the flavonoid curcumin (diferuloylmethane) and various volatile oils, including tumerone, atlantone, and zingerone. Other constituents include sugars, proteins, and resins. The best-researched active constituent is curcumin, which comprises 0.3–5.4% of raw turmeric.95

3.7.1. Medicinal properties of _C. longa_

Some plants such as _Curcuma longa_ contain a natural polyphenol and non-flavonoid compound called curcumin. Curcumin is known for its several biological and medicinal effects, such as anti-inflammatory, antioxidant and so on. Curcumin therapeutic potential for neurodegenerative diseases has garnered great interest in recent years.6 Kulkarni reported that curcumin water soluble extract is able to raise dopamine, norepinephrine and 5-HT levels in CNS.96 Curcumin extracted from _Curcuma longa_ have been reported to have inhibition effects on PD, ROS production, apoptosis, platelet aggregation, cytokines production, cyclooxygenase enzyme activity, brain oxidative damage, cognitive deficits in cell culture and animal models.97,98 The protective effects of _C. longa_ extract (1000 mg/kg, body weight, per oral) on oxidative99 and renal damage have been reported.100 It has been reported that administration of curcumin (50, 100, 200 mg/kg) ameliorated cognitive deficits and mitochondrial dysfunctions symptoms in mice.101 Curcumin has also been indicated.

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**Fig. 1.** Different mechanism of medical properties of medicinal herbs. GSH, glutathione; SOD, superoxide dismutase; CAT, catalase; NO, Nitric oxide; MDA, malondialdehyde; PLA2: Phospholipase A2; PGE2: Prostaglandin-E2; IL-1β, Interleukin-1β; COX-1, Cyclooxygenase-1; iNOS, Inducible nitric oxide synthase.
to exert neuroprotective effects in neuronal degenerative disorders and cerebral ischemia.\textsuperscript{102,103} Scientific evidences demonstrate that curcumin protects the rat brain against focal ischemia through upregulation transcription factor Nrf2 and HO-1 expression.\textsuperscript{104} Additionally, researchers suggested that curcumin debilitates glutamate neurotoxicity in the hippocampal of rat via suppressing ER stress-related TXNIP/NLRP3 inflammation activation.\textsuperscript{105} Linlin et al. also proposed that curcumin protects rats brain against cerebral ischemia-reperfusion injury through increasing neuron survival rate, inflammatory cytokine activity and activating JAK2/STAT3 signaling pathway.\textsuperscript{106} It has been suggested that curcumin protects the brain against oxyhemoglobin-induced neurotoxicity and oxidative stress in vitro model of subarachnoid hemorrhage (SAH) (Xia L).\textsuperscript{107}

The neuroprotective effects of curcumin in PD also are related to its antioxidative properties. Wang reported that curcumin restor ROS intracellular accumulation\textsuperscript{108} in human cell line SH-SYSY exposed to 6-OHDA.\textsuperscript{109} Administration of curcumin (60 mg/kg, body weight, per oral) for three weeks has amended striatum neuronal degeneration in 6-OHDA lesioned rats.\textsuperscript{110} Curcumin protected the neurons against ROS via restoring the GSH decreased levels.\textsuperscript{111} Curcumin increased SOD levels in the lesioned striatum of 6-OHDA mice and MES23.5 cells induced the neurotoxin 6-OHDA.\textsuperscript{112} Curcumin has been reported to protect the axons against LPS degeneration.\textsuperscript{113} Curcumin neuroprotective effects might be mediated by overexpression of BCI-2 which is inducible nitric oxide synthase (iNOS) antagonist. Therefore, curcumin is effective in improvement of NO-mediated degeneration.\textsuperscript{114} Oral administration of 150 mg/kg/day curcumin for 1 week reduced pro-inflammatory cytokines such as IL-6, IL-1β, TNF-α and total nitrite generation in the striatum of MPTP-induced mice.\textsuperscript{115} Furthermore, curcumin decreased activation of NF-κB in LPS\textsuperscript{116} and 6-OHDA-induced inflammatory.\textsuperscript{117}

### 4. Medicinal properties of medicinal herbs and their clinical application

Different medicinal plants showed the antioxidant and anti-inflammatory effects which may have potential therapeutic effects in various nervous system disorders. The results of studies also imply that beneficial effects of the plants on neurodegenerative disorders such as Alzheimer and Parkinson disease are mainly due to the interactions with the cholinergic, dopaminergic and glutamatergic systems. Regarding the anticonvulsant, analgesic effects of the plants interaction with the GABA and opioid system might be suggested. Different mechanism of medical properties of medicinal herbs was summarized in Fig. 1. The effectiveness of medicinal plants on different disorder as clinical studied were showed in Table 1.

5. Conclusion

In this review we propose to focus on neurotoxicity in various studies (\textit{in vitro} and \textit{in vivo}) and investigated the effects of medicinal plants on neural system. The mentioned medicinal plants play their protective roles via increased SOD and catalase levels, restoration of GSH, decreased MDA levels and also protects of neurons against ROS as antioxidant activities. Some protective effects of these natural compounds may be due to reduction of Ca\textsuperscript{2+}, Na\textsuperscript{+} and enhancement of K\textsuperscript{+} level or ‘anti-glutamatergic’ effect. The neuroprotective effects of the mentioned plants occur via reduction of inflammatory cytokines as well as enhancement of anti-inflammatory cytokines, inhibition of the acetylcholinesterase activity and decreased MDA levels in the neural system via modulating GABAergic and glutamatergic neurons, and also increasing amount of amino acids and serotonin (5-HT) in the neurotransmitters systems. Furthermore, the data of the basic and clinical evidence indicated that anti-inflammatory, antioxidant and immunoregulatory effects of some herbs on various disorders. This findings help to recommend the use of these herbs and main compound from natural resources for drug development and more investigation in the clinical studies for future were suggested.

**Conflict of interest**

There is no conflict of interest in this study.

**Acknowledgment**

We are thankful to the Research Council of Mashhad University of Medical Sciences for the partial support of this study.

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