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NATURAL PLANT HERBS USED AS NEUROPROTECTIVE AGENT

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Abstract:-

Neurodegeneration refers to a condition of neuronal death occurring as a result of progressive disease of long-term and is becoming a major health problem in the 21st century. Neurons degenerated are not replaced resulting in a cognitive loss, many neurodegenerative disorders, such as schizophrenia, depression, Alzheimer's disease (AD), dementia, cerebrovascular impairment, seizure disorders, head injury, parkinsonism. The common pathology of neurodegeneration includes deposition of misfolded proteins such as amyloid-β (Aβ) in Alzheimer's disease, α-synuclein in Parkinson's disease (PD), transactive response DNA-binding protein 43 (TDP-43) in dementia. Neuroprotection refers to the strategies and possible mechanisms that are able to protect the central nervous system (CNS) against neuronal injury and neurodegenerative disorders. The past decade has witnessed an intense interest in herbal plants having long-term health-promoting or medicinal qualities. Comprehensive research and discovery have demonstrated that natural products, medicinal herbs, plant extracts, and their metabolites, have great potential as the neuroprotective agent. Although the precise mechanisms of action of herbal drugs have yet to be determined, some of them have been shown to prevent formation of beta-amyloid plaques, promote nerve growth, some inhibit acetylcholinesterase (AChE) enzyme and malondialdehyde (MDA) formation in brain while other exhibits antioxidant activity by increasing the level of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx). Thus the herbal plants can be a valuable source of the drug against neurodegenerative disorders which will require high-throughput screening. This review will highlight the role of herbal plants and their phytoconstituents against neurodegenerative diseases and other related disorders, focusing on their mechanism of action and therapeutic potential.

keywords:- Neurodegenerative disease, Neuroprotective, Herbal Medicine.

Introducation: - Neurodegenerative diseases are characterized by progressive dysfunction and loss of neurons leading to the distinct involvement of functional systems defining clinical presentations. Neurodegeneration is a process involved in both neuropathological conditions and brain aging. It is known that brain pathology in the form of the cerebrovascular and neurodegenerative disease is a leading cause of death all over the world, with an incidence of about 2/1000 and an 8% total death rate .

Neuroprotection is a term used to refer to strategies and relative mechanisms that shield the central nervous system (CNS) from neuronal injuries caused by chronic (e.g., Alzheimer's and Parkinson's diseases) or acute (e.g., stroke) neurodegenerative diseases (NDs). These acute or chronic diseases result from breakdown and deterioration of neurons of the CNS and often result in the deterioration of the cognitive as well as the intellectual faculties of the sufferers. The onset of NDs symptoms is usually gradual as well as progressive and includes loss of memory, primarily short-term, difficulty in learning, motor coordination, and many other functional loses. Ageing, defined as a complex physiological process involving both morphological and biochemical changes that progressively unfold as we get older, has been found to be closely associated with NDs. Ageing stands out as a major

risk factor among the other etiological factors of NDs, including hypertension, genetic and/or environmental factors, and infections. With increasing age, aggregation of proteins, inflammation, oxidative stress, and loss of neurotransmitters, which are common to the pathology of NDs, also occur more often.

Numerous natural products, but primarily plants extracts, have been reported to be used in traditional medicine for neuroprotective, memory enhancing, and antiageing purposes. Examples of such plants include *Ginkgo biloba*, *Panax ginseng*, *Curcuma longa*, *Bacopa monnieri*, and *Salvia officinalis*. These plants have been studied to confirm the traditional claim with special attention given in understanding the mechanism by which they elicit the neuroprotective effects.

Overview of Neurodegenerative Diseases

Neurodegenerative disease is a term used to refer to various conditions which occur as a result of neuronal cell death, particularly, those of the CNS. This deterioration is often associated with gradual onset of progressive symptoms, a major symptom being loss of memory. The NDs include Alzheimer's disease (AD), Parkinson's disease (PD), Lewy body dementia, multiple sclerosis, amyotrophic lateral sclerosis (ALS), and spongiform encephalopathy. Of these NDs, AD is the most prevalent, accounting for over 60–70% of all forms of dementia. Protein aggregation, inflammation, excitotoxicity, oxidative stress, and neurotoxicity have been implicated in the pathophysiology of NDs.

Alzheimer's Disease

The AD is the most prevalent and devastating disorder of the NDs. It is an incurable disease of cognition and behavioral impairment that affects social and occupational activities and is also a leading cause of institutionalization in the elderly. Clinically, AD is characterized by a progressive and irreversible memory deficits, cognitive deterioration, and personality changes, with a mean duration of about 8.5 years between onset of clinical symptoms and death. Memory impairments are first to appear in the early stage of the disease, after which motor and sensory functions are affected as the disease progresses. The onset of AD is usually above 65 years of age, with risk from this age doubling every 5 years. Hence, it has been suggested that the risk for AD for persons living into their eighties rises to 20–40% depending on a variety of factors such as population dynamics and geography. As the world population continues to age in parallel with economic development, the number of people with NDs and the associated dementia also continues to increase. This increase has in turn prompted an enormous increment in research interest and efforts on the discovery of new therapeutic agents for primary, auxiliary, or tertiary prevention of these diseases.

Parkinson's Disease

The PD is the second most common ageing-related neurodegenerative diseases that can greatly impair quality of life with significant consequences in terms of cost of patient care. Primarily a movement disorder, as opposed to AD which is mainly a cognitive disease, PD affects approximately 1% of the human population over the age of 60. Its classical signs include resting tremors, bradykinesia, extrapyramidal rigidity, and loss of postural reflexes such as disturbance in walking or equilibrium. The PD involves loss of dopaminergic neurons of the pars compacta region of the substantia nigra and their terminals in the corpus striatum. Since neurodegeneration is not restricted to the basal ganglia, PD is also linked with nonmotor disorder like dementia. The association between PD and oxidative damage of neuronal cells has been well established. For example, the breakdown of dopamine (DA) by autooxidation has been shown to be linked to semiquinone metabolism and the generation of superoxide anion, hydrogen peroxide (H_2O_2), and monoamine oxidase (MAO) expression.

Other Neurodegenerative Diseases

Amyotrophic lateral sclerosis is thought to be caused by the mutation of the gene coding for the enzyme superoxide dismutase (SOD) and also by the misfolding of the same enzyme. The ALS is incurable and has generally a median survival of three years from onset to death. Its symptoms include tripping or stumbling when running, foot and wrist drop, slurred speech, and depression. Huntington disease (HD) is another incurable ND. It has an adult onset with autosomal dominant inherited disorder characterized by progressive brain degeneration, causing rapid deterioration and eventually death. Symptoms of the diseases include involuntary movement, dementia, and behavioral changes.

Ageing

Ageing has been defined as a complex physiological process involving both morphological and biochemical changes that occur

progressively. These changes include those of the CNS, the skin, the cardiovascular system, and hormonal and reproductive systems. Ageing remains to be the leading risk factor for NDs except for the familial forms which are found to affect individuals younger than 60. Human life expectancy has increased rapidly over the past decades especially in developed countries, and as the world populations get older, age-related NDs such as AD and PD have become more common.

Neuroprotective effects of medicinal plants :

1.Crocus sativus-

Crocus sativus L (C. sativus), commonly known as saffron belongs to the Iridaceas family, Crocoideae superfamily which is cultivatedin many countries including Iran, Afghanistan, Turkey and Spain.15VMSaffron consists dried and dark-red stigma with a small portion ofthe yellowish style attached of C. sativus. It used mainly as herbalmedicine in various regions in the world.16 saffron possesses 150 different compounds including carbohy-drates, polypeptides, lipids, H2O, minerals and vitamins. Crocins arethe main biologically active ingredients of saffron, a family of red-colored and water-soluble carotenoids, which are all glycosides of Crocetin. Also, saffron has four main bioactive components such as,crocin, crocetin, picrocrocin and safranal. Another constituent ofsaffron was Picrocrocin which has a bitter taste

1. Medicinal properties of C. sativus : In Iranian traditional medicine, Crocus sativus is used to treat cognitive disorders. Recently C. sativus constituents were used totreat some neural disorders and to relax smooth muscle.18e20 The anticonvulsant and anti-Alzheimer properties of saffron extract in humans and animal models have been reported.18 The efficacy of C. sativus in the treatment of mild to moderate depression in clinical trial studies, and effect on brain neurotransmitter concentrations as well as its interaction with the opioid system were reviewed.18 C. sativus and its main component, crocin, possess potent antioxi-dant effects via reducing of MDA level.21,22 The administration of C. sativus extract (100 mg/kg, p.o.) before induction of cerebral ischemia by middle cerebral artery occlusion (MCAO) significantly reduced glutamate and aspartate concentrations, SOD, catalase and K-ATPase activities induced by ischemia in rats.23 In addition, administration of C. sativus extract (200 mg/kg) and honey syrup for 45 days reduced the aluminum chloride-induced neurotoxicity in mice.24 Administration of C. sativus (30 mg/day) for 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.26 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 imip- ramine (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.

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.30 The major phenolic compounds of N. sativa seeds are p-cymene (37.3%), Thymoquinone (TQ) (13.7%), carvacrol (11.77%), and thymol (0.33%).

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 pro- tective 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 improvedVscopolamine e 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,BMDA and NO. N. sativa also improved inflammatory responsesIP **a**nd 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) 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 and some other oxygenated monoterpenes and monoterpene hy- drocarbons. 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 (60e70%) and 20% hydrocarbons but the composition of the herb oil was completely differs from the seed oil.

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-rheumatoid effects. In Iranian traditional medicine, C. sativum has been suggested to relive 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 andSpain.15 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.16 Saffron possesses 150 different compounds including carbohydrates, polypeptides, 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 crocetin. Also, saffron has four main bioactive components such as, crocin, crocetin, picrocrocin and safranal. Another constituent of saffron was Picrocrocin which has a bitter taste.

4. Ferula assafoetida

Asafoetida (F. assafoetida L.) belongs to the Apiaceae family which obtained from the exudates of the living underground rhizome or tap roots of the plant. F. assafoetida 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 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.

Medicinal properties of F. assafoetida

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 . In pharmacological and biological studies, the ole-gum-resin of Ferula asafoetida have been revealed to have antioxidant,antiviral, antifungal, anti-diabetic, molluscicidal, antispasmodic and antihypertensive 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 acetylcholinestrase (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.66 In behavioural models, such as elevated plus maz, 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.

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 com- ponents of TV. It was contains less amounts of phenol during the winter. Also, thymol methyl ether (2%), cineol, cymen, pinene, borneol and esters are components in the essential oil.

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, antispasmodic, and expectorant effects. Researchers have reported that tocols and phenolic in thymus vulgaris oil (TO) can directly react with free radicals and inhibit lipid peroxidation. It has been also reported that treatment

with thymol results in improvement of antioxidant status in rat brain. In addition, the results of behavioural studies have demonstrated that the extract of thyme can induce anxiolytic effects in rat when it was orally administered for 1-week. In confirmation of this report extract of thyme enhances the percentage of both the entries and the time spent in the open arms of the maze. The results of animal studies also revealed that kaemfrol in thyme extract applies anxiolytic effects in the elevated plus maze (EPM) in mice. Carvacrol derived from this plant has also been indicated to have anxiolytic effects in the plus maze test. Bioactive monoterpenes in thyme extract such as linalool have been reported to be able to decrease the level of anxiety in animals. The essential oil of thyme has also been suggested to have a dose dependent protective effect against toxicity of alfatoxins. In addition, it has been documented that thymol acts centrally via mimicking or facilitating GABA action and modulates GABAA receptor. Therefore, it can apply the significant anticonvulsant and antiepileptogenic effects. Recently, neuroprotective and improvement effects of thymol, a bioactive mono- terpene isolated from thymus vulgaris, on amyloid b or scopolamine-caused cognitive impairment in rats was documented. Researchers have suggested that neuroprotective effects of thymol can attribute to its potential effect on GABA-mediated inhibition of synaptic transmission. Meanwhile, researchers reported that TO could modulate cholinergic function via enhancing synaptic acetylcholine (Ach) and nicotinic Ach receptor activity. Additionally, antidepressant effects of thymol were documented. Deng et al. reported that thymol administration significantly 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.

◆ **Medicinal properties of medicinal herbs and their clinical application**

Different medicinal plants showed the antioxidant and antiinflammatory 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

Natural plants Herbs & drug used as a neuroprotection in ischemic stroke:

Picture	Plants Species	Parts used	Geographi Location
	Leaves, Stem	Leonurus heterophyllus	Lamiaceae
	Leaves, Seeds	Ginkgo biloba	Ginkgoace
	Fruit	Fructus chebulae	Combreta
	Fruits,Seeds	P.granatum	Lythracea
	Flower	R.laevigata	Rosaceae
	Fruits	A.sativum	Amarylld
	Roots,Bulb, Leaves, Seed	Allium cepa	Amaryllid ae

	Fruit, Leaves	Grape	Vitaceae		Lepidium meyenii	Diarrhoea, Hepatitis	Roots	South America
	Fruit, Leaves	O.europaea	Oleaceae		Convolvulus pluricaulis(shankhpushi	High cholesterol,heartdisease	Whole plant,Roots,seeds	India

ROLE OF MEDICINAL PLANTS AGAINST ALZHEIMER'S DISEASE:-

Natural medicines against dementia :-

Herbs	Plant Species	Parts Used	Geographical location	Uses	Family
	Centella asiatica (Gotu kola)	Leaves	India, Srilanka,Bangladesh	sclar skin	Apiaceae
	Glycyrrhiza gabra	Roots & Rizome	South-Western Asi	gh,	Fabaceae
	Curcuma longa (Turmeric)	Tuberous rhizome, undergroud st.em	South –East Asia	Respiratory problems	Zingiberaceae
	Bacopa monnieri (Brahmi)	Whole Plant	Europe, Asi	's g memory	Scrophulariaaeae
	Ginkgo biloba	Leaves	China	Loss,	Ginkgoaceae
	Withania somnifera (Ashwagandha)	Whole plant	Afganisthn, orth America,Sri Lanka	depression	Solanaceae
	Magnolia officinalis	Bark	China	Digestive system	Magnoliaceae

Pictures	Class of the compound	Name of the compound	Source
	Steroidal alkaloid	Galantamine	Galanthus nivalis
	Steroidal alkaloid	Assoanine	Narcissus assoanus
	Quinolizidine alkaloid	(-)-Huperzine A	Huperzia serrata
	Indole alkaloid	Physostigmine	Physostigma venenos
	Cynatroside A	Pregnane glycoside	Cynanchum atratum
	Isoquinoline alkaloid	Corynoline	Corydalis incisa

	Glycoalkaloid	α-Solanine	Solanum tuberosum	Solanaceae	44.3% inhibition at 10 uM
	Stilbene oligomer	(+)-α-Viniferin	Caragana chamlague	Leguminosae	50% inhibition at 2.0 μM

Conclusion :-

The management of neurodegenerative diseases remains a challenge in the modern medicine because of their complicated pathogenesis. Protein misfolding and their accumulation inside or outside of neurons is the key pathological feature in several neurodegenerative diseases including Alzheimer's, Parkinson's Huntington's disease. Herbal medicines are regarded as effective and promising sources of potential neuroprotective agents because of their cognitive benefits and more significantly, their mechanisms of action with respect to the fundamental pathophysiology of the diseases. Our review has acknowledged several herbal medicines such as such as Allium sativum, Ginkgo biloba, panaxginseng, Terminalia chebula with potential therapeutic effects for neurodegenerative diseases

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