Brief Report

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Medicinal Herbs Effective in the Treatment of the Alzheimer's Disease

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ABSTRACT

BACKGROUND AND OBJECTIVE: Alzheimer's is a progressive brain disorder which will gradually damage the memory, reduce learning and reasoning ability, impair judgement and communication and interfere with daily activities. As Alzheimer's advances, patients may experience changes in their behaviour and personality. Such examples are anxiety, feelings of suspicion, consternation and delusional visions. Currently, there is no available treatment for this illness. Nevertheless, new approaches have extended horizons about the biology of this illness. Alzheimer's is the most prevalent type of brain deterioration affecting over 20 million people across the world. In this article, we investigated the findings of previous control studies in order to determine whether medicinal herbs could be effective in treating cognitive disorders caused by this illness in the elderly. Furthermore, a few common medicinal herbs for treating Alzheimer's have been looked into in this article.

METHODS: In this study, we conducted investigations into the studies done on Alzheimer's using databases such as Scopus, Web of Science, SID, Pumbed Central, Pumbed and a number of key words like Alzheimer's, medicinal herbs, Acetylcholine and antioxidants.

FINDINGS: The first neurotransmitter deficiency discovered in Alzheimer's was Acetylcholine which is a cholinergic neurotransmitter necessary for the short-term memory. Cholinergic deficiency due to Alzheimer's is mainly responsible for the problems of short-term memory.

CONCLUSION: Undoubtedly, cholinesterase inhibitors and NMDA receptor antagonists are efficacious in treating Alzheimer's. However, these treatments are unlikely to impede the illness and they tend to lose their effectiveness in the long run. The products of medicinal herbs are mostly used in treating the psychological and behavioural symptoms of Alzheimer's.

KEY WORDS: Alzheimer's Disease; Medicinal herbs; Acetylcholine; Antioxidant.

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Introduction

Premature delivery occurs before the completion of 37 weeks of pregnancy (1). In many industrialized countries, preterm birthrates are experiencing an increasing trend. For instance, the incidence has risen from 5.9% in 1981 to 12.7% in 2005 in the United States of America (2). According to two studies conducted in Tajrish Martyrs Hospital in Tehran and Bandar Abbas, the incidence of premature delivery was reported to be 7.23% and 4.4%, respectively (3, 4). Nowadays, with the remarkable progress in the identification of risk factors and mechanisms associated with premature birth, reducing the rate of this condition through medical interventions and public education on pregnancy health has been a primary goal in the field of medicine (2,5). Premature birth is considered to be responsible for 75% of perinatal deaths and it is the sole cause of more than 50% of long-term morbidities. Although many preterm neonates might survive, they will be prone to a severe risk of developmental disorders of the nervous system, respiratory and sensory impairment, learning disabilities and digestive complications (6,7). Thus, several studies have partially examined the risk factors for premature delivery.

In their study, Silveira et al. claimed that such factors as black skin color, lower degrees of education, lower income, teenage pregnancy, history of premature delivery, smoking and employment during pregnancy are likely to significantly raise the risk of premature delivery (8). In another research, Yuan et al. also found that such factors as a history of premature delivery, the mother's age (over 39 years), socioeconomic issues, smoking during pregnancy, hypertension, mental disorders and abnormal uterine are known to be significantly associated with the incidence of premature delivery (9).

In another study, these factors were determined as early age, the state of being a single mother, the mother's degree of education, body mass index (BMI), lower income, the history of abortion and a history of premature births (10). For another thing, preterm neonatal births bear a heavy cost on the health care system of a country. Investigating several studies in this regard has revealed that there are differences in the risk factors for premature delivery depending on the geographical situation and racial diversities across the world. Since only a few studies have attempted to survey the risk factors for premature delivery in the city of Babol, this study aimed to evaluate the prevalence of such factors.

Methods

This cross-sectional study was conducted in the maternity ward of Ayatollah Rohani Hospital affiliated with the Babol University of Medical Sciences which is a principal referral center for women with high-risk and premature pregnancies. The sample size was determined on the basis of previous studies. In the present study, 377 pregnant women with premature delivery (23-37 weeks of pregnancy) and 423 sample term pregnant women were enrolled from 2011 to 2013. Upon obtaining permission from the Ethics Committee of the Medical University of Babol, written consent was provided from the subjects. Through interviewing the mothers, the initial maternal data were extracted including the age, gravidity and parity, any history of abortion, BMI, mother's degree of education and occupation, any history of infertility, smoking habits and the use of alcohol and drugs, consumption of fast food (more than twice a week), the age of pregnancy, cervical cerclage, cell phone use, any history of diseases in the mother (e.g anemia, cardiovascular diseases, diabetes, hypertension and thyroid and psychiatric disorders) (11, 12), any history of surgery, Urinary Tract Infections (UTI), Oligohydramnios, intrauterine growth restriction (IUGR), embryonic anomalies, premature rupture of membranes and vaginal bleeding. Eventually, the infants' data were recorded by a neonatal specialist including birth weight, need for resuscitation and hospitalization, 5-minute Apgar scores and the mortality rate of the hospitalized neonates. The collected data were analyzed and compared by SPSS software V.18, T-test, Chi-square, Fisher's exact test and Mann-Whitney. The $p<0.05$ was considered as significant

Results

Alzheimer's Disease (AD) is an irreversible, progressive brain disorder which occurs through a gradual process resulting in memory loss, acting abnormal, behavioural changes and the reduction of thinking ability (1). The disease starts with the person's losing his short-term memory as in forgetting addresses and names and shortly, the person might not even be able to remember his way back home.

Although certain medications are available for Alzheimer's, it is not yet possible to impede the disease's progress. Scientists believe that Alzheimer's appears in most cases due to a combination of inheritance, lifestyle and environmental factors

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deteriorating the brain steadily (2). According to many studies, the number of AD patients will probably be tripled in 50 years time. For the time being, the average cost for each AD patient is estimated to be 150 thousand dollars and it is anticipated that this figure will rise over 450 thousand dollars in the near future (2).

It is acknowledged that Alzheimer's disease will be affecting more than 15 million people around the world and it is the major cause of brain deterioration among the elderly. Alzheimer's disease is a progressive brain disorder which lasts for an average of 8.5 years starting from the onset of clinical symptoms to the patient's death. Certain regions of the brain that are related to mental functions, especially neocortex and hippocampus, are the ones most affected by the pathological hallmark of AD (3). There are several hypotheses explaining the onset of this disease: cholinergic hypothesis and the hypothesis of Amyloid formation. At the moment, the most widely accepted clinical strategy for AD is using Cholinesterase inhibitors. These inhibitors can obstruct the Acetylcholinesterase enzyme in order to increase the level of acetylcholine in the brain. Acetylcholinesterase inhibitors include Rivastigmine, Tacrine, Donepezil and Galantamine while N-methyl-D-aspartate (NMDA) receptor antagonists (memantine) are already prescribed as well. Nevertheless, there is no definite treatment for AD except for managing the symptoms (4).

These findings intrigue us to do further research on the factors that are able to increase the level of acetylcholine in the brain. Choline acetyltransferase enzyme activities or cholinergic neurons in the front section of the brain's basal are seen to decrease in the brains of AD patients. Such damages are associated with cognitive disorders (5). Since the cholinergic branches are sent to the cortex and septum from Nucleus basalis of Meynert (NBM), the electrical destruction of NBM causes the death of cholinergic cells in this cortex decreasing the level of acetylcholine in the cortex (6). Recent studies indicate that AD is accompanied with inflammatory processes. Reactive Oxygen Species (ROS) damage cellular components and act as secondary carriers in the inflammation. In such cases, antioxidants could contribute to treating AD (7).

Oxidative stress, which is the imbalance between free radicals and the antioxidant system, plays a key role in the pathogenesis of this disease. Oxygen free radicals can invade proteins, nucleic acids and lipid membranes consequently disrupting the cell functions. The brain tissue contains large amounts of polyunsaturated fatty acids which are vulnerable to the oxygen free radicals. It seems that significant lipid peroxidation is specifically a destructive form of oxidative neuronal damage. It harms the membrane and generates several secondary products. Both the split form and the ring form of oxygenated fatty acids are known to have neurotoxic effects (8). The treatment of AD is principally pharmacological. Recognizing the duration of the disease as well as the improvements and the conducted clinical experiments makes it possible to enhance the treatment of cognitive and non-cognitive symptoms. The pharmacological treatment strategy of AD consists of three major categories:

1- Medications which are based on disease-modifying therapies like vitamin E and Selegiline;

2- Treatments which are based on compensating for neurotransmitters like using cholinesterase inhibitors;

3- Psychotropic factors which are prescribed for behavioural symptoms of the disease (9).

Although certain synthetic medications have recently been suggested for treating memory and learning disorders, they exert little influence on the patient and many of them are known to have adverse side effects. Recently, there has been a growing interest in the traditional medicine. In the present study, we examined the medicinal herbs which had the primary therapeutic signs for AD symptoms. One thing these herbs have in common is their neuro-protective agents which act through inhibiting the Acetylcholinesterase enzyme or the oxidative stress. Recent studies confirm medicinal herbs to be capable of treating or preventing several disorders like memory problems (10), strokes (10-16), digestive issues (17) and other problems.

Although such effects could be related to other specific materials in these herbs, they are mostly associated with the antioxidant properties. The anti-dementia mechanism of these herbal extracts and their combinations is not fully comprehended. To the best of our knowledge, a number of the medicinal herbs in the present study activate the central acetylcholine through inhibiting acetylcholinesterase enzyme and stimulating the synthesis of acetylcholine. While the recently introduced cholinesterase inhibitors like Tacrine and Donepezil are known to reduce the number of AD patients and develop signs of relief, the majority of these patients have not yet benefited from the major financial investments in research and development programs in this area (18). The impairment of the memory and learning ability caused by brain deterioration could be chemically infused in clinical animals by Scopolamine.

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Scopolamine is a known cholinergic antagonist which interferes with the transmission of acetylcholine in the central nervous system (19).

This transmission terminates upon the hydrolysis of acetylcholine by the acetylcholinesterase enzyme which is responsible for the deformation of acetylcholine into acetate and choline in the synaptic cleft (20). Animal models of Scopolamine-induced amnesia are widely used in the search for compounds of potential therapeutic properties for brain deterioration (21).

Being able to imply the cognitive impairments caused by AD, NBM patterns are applicable in studying the role of cortical cholinergic function in awareness and understanding (22). Furthermore, animal models demonstrate the cholinergic markers through NBM. These markers include the acetylcholine level, acetylcholine release and conversion, acetylcholine reabsorption, Acetylcholinesterase activities and the number of Muscarinic cholinergic receptors in the frontal cortex (23). The increasing level of Malondialdehyde (MDA) is recognized as a reactive oxidative type as well as a reliable indicator of lipid peroxidation in vivo (24). Extensive research is being conducted on different herbs worldwide. The therapeutic effects of herbal medications outnumber their side effects and they are also more economical. Moreover, herbal extracts are likely to provide a source of new compounds similar to many chemical drugs which are initially derived from herbal resources.

Hypericum perforatum: Hypericum perforatum is a gramineous, perennial plant with an average height of 30 to 90 centimetres. It is a creeping plant with glabrous stems. The leaves are spoon-shaped with no petiole. Hypericum perforatum has numerous essence cavities which have inspired the name.

The stems, flowers and leaves of this plant contain a variety of compounds like essence, Tannin, Hypericin, Hyperin, Choline and Flavonoids. Clinically, this herb is known to have antidepressant properties and it is able to treat some neurological disorders. It is an anxiolytic, anti-inflammatory, analgesic herb with wound healing agents (25). The extract of Hypericum perforatum contains such Flavonoids as Quercetin which is able to inhibit free radicals. The antioxidant properties of Quercetin are also detected in the inhibition of lipid peroxidation (26). In a study, the impairments of memory and learning were investigated through the acute injection of 4.1 mg of Scopolamine in rats. This dosage normally leads to certain changes in the level of oxidative stress in the brain while increasing the MDA level. The findings of this study indicated that Scopolamine noticeably increased Glutathione peroxidase and reduced the level of Glutathione in the brain. These are the main factors resulting in the increasing levels of oxidative stress in the brain. Furthermore, when the glutathione level in the brain increases, it directly leads to a decrease in the Reactive oxygen species (ROS) level. Pre-treatment with doses of 4, 8, or 12 mg of Hypericum perforatum 30 minutes before injecting Scopolamine ignites the antioxidant activity through influencing the MDA level and the glutathione of the brain and affecting the activity of glutathione peroxidase in the brain (24).

In mice, continuous injection of hypericum perforatum extract and its effective substance called Hyperforin was found to improve passive avoidance learning by the ShuttleBox system (27). As an antioxidant, the extract of this herb could be prescribed as a new, effective antidepressant with memory-enhancing features (24).

Lepidium Meyenii: Lepidium meyenii grows at an altitude of 3500 to 4500 metres in the Andes in Peru. It is a rare species able to survive in the harsh conditions of Andes under the burning sun, during long hot days, cold nights and dry winds. In a study, the effects of different doses of the hydraulic and Ethanol extracts of this herb was studied through infusing learning and memory impairments on rats by 1 milligram of Scopolamine for 35 days. The results indicated that Lepidium meyenii improves the impairments of spatial memory and learning as well as the impairments of passive avoidance memory and learning caused by Scopolamine. In this study, Scopolamine increased acetylcholinesterase in the rats' brains 1.5 fold while the Lepidium meyenii extract increased the level of acetylcholinesterase enzyme by 45% more than the group which received only Scopolamine.

Prunella vulgaris: For the most part, Prunella vulgaris spreads across South Korea, Japan, China and Europe. This plant is still used in the traditional Chinese medicine for treating inflammation, eye pain, headaches and dizziness (28). According to previous studies, Prunella vulgaris contains several active compounds such as Oleic acid, Betulinic acid, Ursolic acid, Flavonoids and Rosmarinic acid (29). Moreover, this plant has antiallergic, anti-inflammatory, anti-oxidative, antimicrobial and antiviral properties (30). Taking 20-25 milligrams of Prunella vulgaris extract improved the secondary delay reduction during the Shuttle Box test on the Scopolamine receiving rats. In addition, Prunella

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vulgaris extract was found to enhance the impairments caused by Scopolamine during the Y-Maze test. Such beneficial effects of Prunella vulgaris are a result of its acetylcholine mimic feature.

The acetylcholinesterase activities are not inhibited by Prunella vulgaris in vivo or ex vivo and the effects of memory improvement are not employed through inhibiting acetylcholinesterase but rather, they are employed via an indirect effect in the cholinergic signalling. In other words, Prunella vulgaris is able to employ its beneficial effects in reinforcing memory and learning through increasing the cholinergic neurotransmitters by NMDA receptor signalling (28).

Cyperus rotundus: This plant belongs to the Cyperaceae family. In the rhizome of Cyperus rotundus there exists a specified essence containing pynn, a little Cineole and a new alcohol called ezosiproll. Several chemical compounds have been taken from the ethanol rhizome extract of Cyperus rotundus some of which result in effective, anti-acetylcholinesterase activities (31). In a study, rats with destroyed NBM core were given two doses of 100 and 200 milligrams of the Cyperus rotundus extract. This extract is known to have anti- acetylcholinesterase properties making it able to reinforce memory, spatial learning and passive avoidance learning (32).

Zizyphus jujuba: Initially, the Jujube fruit is green but it turns red and gets wrinkly when it ripens. This fruit has a long, thin core and it fully ripens in the autumn. It is an edible plant with a sweet taste and numerous medicinal features. Jujube is relaxing and anti-grouch and it was used in the traditional Chinese and Korean medicine in order to reduce anxiety, refine the spleen and stomach and enhance the digestive system (33). The compounds that could be extracted from this fruit are tri tip noida, Flavanone and alkaloid. Additionally, a phenyl glycoside combination called Zizyphus is extracted from this fruit (34). Studies show that this herb contains active compounds which have inhibitory effects on releasing Antihistamines and activating acetyl cholinesterase and Cyclooxygenase I and II.

Moreover, this plant has cytotoxic agents that can activate biological compatibility. Jujube's seed contains large amounts of Mucilage, Maleic acid, Citric acid, sugar, protein, minerals and Vitamin C (35-37).

By refining eight kinds of Flavonoids from Jujube, its medicinal properties are partly attributed to the antioxidant features of these compounds. Among the 50 species of plants studied here, the Jujube extract was proven to be the most effective on activating acetylcholine transferase (34/1%) in vitro. Furthermore, a compound was found in this extract with the same effect called Cis-9-Octadecenamide or Oleamide (38). It is possibly because of this feature and the increasing acetylcholine levels in the cholinergic terminals that improvements are seen in the Alzheimer's symptoms and motor impairments. For another thing, the Ethanol extract of Jujube has a restorative effect on the memory and learning, motor coordination and the behavioural disorders caused by the destruction of the Meynert core in the front base of the rats' brain.

The aforementioned could be a result of the activating feature this extract has on acetylcholine transferase. It can lower the treatment costs of mental and motor disorders in AD patients while used as a proper supplementary medication for chemical or artificial drugs that have adverse side effects.

Lavandula Officinalis: This plant is widely referred to as "lavender" and since ancient times, it has drawn the attention of health practitioners. As an aromatic herb, lavender has been widely circulated. Its flowers and essence has been used in cosmetics and perfume industry. This plant is of the Lavandula genus. The leaves are similar to Savory leaves yet longer and thinner and it has whitish flowers (40). So far, 48 species of this plant have been identified in different spots of Southern Europe and Mediterranean countries, especially in the south of Italy, Yugoslavia, Greek, south of France and North Africa. It is not categorized as a wild herb in Iran so it does not grow by itself. Nevertheless, it has recently been planted in certain regions of our country. Lavender has purple flowers in the form of clusters. The flowers, as well as the tip of the stems, are the usable parts of this herb. Lavender has a very desirable smell and a bitter taste and it has been used in making perfumes for its fragrance.

Lavender's essence is the result of the instillation of its flowers and stem tips. This essence is yellow or greenish with a pleasant smell. According to investigations on this subject, there have not been adequate studies conducted on the phytochemical characteristics of this plant up until now (41).

Several compounds have been discovered in this herb. Such examples are Geraniol, Linalool, Linalyl acetate, Borneol, alpha-Pinene, Camphor, Butyric acid, Valeric acid, Ursolic acid and Flavonoid Luteolin. These compounds affect the regions of the central nervous system in a relaxing and calming fashion through GABA receptors (42). Treatment by the essence of lavender can considerably reduce the level of neurologic deficit, strokes, MDA, carbonyl and ROS in

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rats exposed to ischemia and revascularization which demonstrates a strong neuro-protective effect (43).

It has been confirmed that activities of acetylcholinesterase and consequently, the decrease of acetylcholine as well as the reduction of synaptic transmission could cause Alzheimer's and loss of spatial memory. The inhibiting effect of lavender extract in different densities on acetylcholinesterase enzyme has been confirmed by tests on cell lines (44).

Moreover, it has been demonstrated that free radicals can cause the peroxidation of phospholipids, DNA damage and denaturation of protein. Hippocampus is the spatial learning area of the brain and long-term potentiation (LTP) is one of the most important cellular mechanisms involved in the spatial memory and the learning process. It has been demonstrated that consuming antioxidants results in improvements in spatial learning and it can also increase the infusion of LTP in rats with Alzheimer's (45). The ethanol extract of lavender enhances spatial and passive avoidance memory and learning as well as the motor balance. Such neuro-protective effects are perhaps rooted in the antioxidant properties of this herb (10).

Morinda citrifolia: Morinda citrifolia is more commonly known as a kind of bread and is dominantly consumed as a food in the tropical regions of Indonesia and Hawaii. This species is a small tree with a straight trunk and it is planted in different regions of India (46). As a popular herb, the juice of Morinda citrifolia is used as a remedy for many diseases such as arthritis, diabetes, high blood pressure, menstrual problems, heart problems, cancer, ulcers, depression and atherosclerosis (47). The extract of the fruit and the leaves of this plant have analgesic, anti-inflammatory and antioxidant properties (48). Moreover, the ethyl acetate extract of Morinda citrifolia is known to prevent memory impairments and oxidative stress caused by Beta-amyloid peptide in rats (46). Treatment with chloroform, ethyl acetate and Butanol extracts of Morinda citrifolia noticeably reduces the acetylcholinesterase enzyme activities in the brains of the Scopolamine receiving rats (49). Furthermore, forgetfulness due to the infusion of Scopolamine is accompanied with the reduction of cerebral blood flow (CBF) and an increase of oxidative stress and acetylcholinesterase enzyme activities in the rats' brains. In such cases, treatment with the Morinda citrifolia extract is proven to enhance memory impairments caused by Scopolamine during the Shuttle Box test (49).

Curcuma longa Linn: Turmeric, under the scientific term of Curcuma longa Linn, wildly grows in tropical regions like India and China. The chemical content of this herb consists of 5% essence and 5% of the main polyphenol ingredient of turmeric called Curcumin. Curcumin is an active compounds with antioxidant, anti-inflammatory, anti-cancer and antibacterial agents which also protects the liver tissues (50, 51). Turmeric belongs to the ginger family scientifically termed as Curcuma longa. It is herbaceous and grows on one to one at a half-meter height. It has a swollen rhizome coming out of some of its aerial stems. The dried rhizomes of this herb are edible and medicinal. Turmeric is a domestic plant in warm parts of Asia; counties like India, Pakistan, Indonesia, south of China and parts of Africa and southern America. Turmeric does not grow in Iran (52). Turmeric reinforces the activities of monocytes and macrophages of the AD patients resulting in the reduction of Beta-amyloid in vivo (53). The antioxidant and anti-inflammatory properties of turmeric along with its ability to adjust the immune system play a pivotal role in improving the metabolism as well as preventing the procedure of cell injury in AD**)**

Discussion

Currently, there are no available treatments for stopping or slowing down the Alzheimer's disease. American FDA has confirmed 5 drugs to be temporarily effective on the symptoms of this disease. However, it should be taken into account that these medications might have different levels of effectiveness in the society. With their cognitive benefits, medicinal herbs have a major role in treating Alzheimer's. More importantly, their functional mechanism with regards to the underlying pathophysiology of the disease based on initial clinical evidence suggests that some of these herbs could enhance memory and learning in people with medium to low levels of AD. Helpful effects of these herbs' compounds are not limited to inhibiting acetylcholinesterase. Enhancing the process of Aβ, protecting against Apoptosis and oxidative stress and having anti-inflammatory effects are other beneficial features of such herbs. Using medicinal herbs in treating AD should be put into comparison with treatments with other drugs in which case further studies are to be conducted in order to determine the effectiveness of these compounds on the Alzheimer's disease.

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References

1.Parihar MS, Hemnani T. Alzheimer's disease pathogenesis and therapeutic interventions. J Clin Neurosci. 2004;11(5):456-67.

2.Herring A, Ambrée O, Tomm M, Habermann H, Sachser N, Paulus W, et al. Environmental enrichment enhances cellular plasticity in transgenic mice with Alzheimer-like pathology. Exp Neurol. 2009;216(1):184-92.

3.Babic T. The cholinergic hypothesis of Alzheimer's disease: a review of progress. J Neurol Neurosurg Psychiatry. 1999;67(4):558.

4.Orhan I, Aslan M. Appraisal of scopolamine-induced antiamnesic effect in mice and in vitro antiacetylcholinesterase and antioxidant activities of some traditionally used Lamiaceae plants. J. Ethnopharmacol. 2009;122(2):327-32.

5.Bartus RT, Dean RL, Beer B, Lippa AS. The cholinergic hypothesis of geriatric memory dysfunction. Science. 1982; 217(4558):408-14.

6.McGaughy J, Decker MW, Sarter M. Enhancement of sustained attention performance by the nicotinic acetylcholine receptor agonist ABT-418 in intact but not basal forebrain-lesioned rats. Psychopharmacology (Berl). 1999;144(2):175-82.

7.Gilgun-Sherki Y, Melamed E, Offen D. Antioxidant treatment in alzheimer's disease. J Mol Neurosci. 2003;21(1):1-11.

8.Bassett CN, Montine TJ. Lipoproteins and lipid peroxidation in Alzheimer's disease. J Nutr Health Aging. 2003;7(1):24-9.

9.Bush AI. The metallobiology of Alzheimer's disease. Trends Neurosci. 2003;26(4):207-14.

10.Rabiei Z, Rafieian-Kopaei M, Mokhtari S, Alibabaei Z, Shahrani M. The effect of pretreatment with different doses of Lavandula officinalis ethanolic extract on memory, learning and nociception. Biomed Aging Pathol. 2014; 4(1):71-6.

11.Rabiei Z, Bigdeli MR, Rasoulian B, Ghassempour A, Mirzajani F. The neuroprotection effect of pretreatment with olive leaf extract on brain lipidomics in rat stroke model. Phytomedicine. 2012;19(10):940-6.

12.Rabiei Z, Bigdeli MR, Rasoulian B. Neuroprotection of dietary virgin olive oil on brain lipidomics during stroke. Curr Neurovasc Res. 2013;10(3):231-7.

13.Rabiei Z, Bigdeli MR, Mohagheghi F, Rasoulian B, Sharifi A. Effect of dietary olive leaf extract on brain cholesterol, ester and triglyceride levels and of brain edema in rat stroke model. Razi J Med Sci. 2013;19(103):18-25. [In Persian]

14.Rabiei Z, Bigdeli MR, Mohagheghi F, Rasolian B. Relationship between dietary virgin olive oil on brain cholesterol, cholesteryl ester and triglyceride levels and blood brain barrier (BBB) permeability in a rat stroke model. Physiol Pharmacol. 2012;16(3):245-54. [In Persian]

15.Rabiei Z, Bigdeli MR, Rasoulian B, Mohagheghi F, Sharifi A. The effect of various doses of olive leaf extract on brain lipid levels and blood brain barrier permeability in rat stroke model. Pajoohandeh J. 2012;17(2):67-72. [In Persian]

16.Rabiei Z, Bigdeli M, Mohagheghi F. Effect of dietary virgin olive oil on infarct volume and brain ceramide, cerebroside and phosphatidylcholine levels in rat stroke model. J Shahrekord Univ Med Sci. 2013; 15(1): 23-31. [In Persian]

17.Moradi MT, Rafieian-Koupaei M, Imani-Rastabi R, Nasiri J, Shahrani M, Rabiei Z, Alibabaei Z. Antispasmodic effects of yarrow (Achillea millefolium L.) extract in the isolated ileum of rat. Afr J Tradit Complement Altern Med. 2013;10(6):499-503.

18.Perry EK, Pickering AT, Wang WW, Houghton PJ, Perry NS. Medicinal plants and alzheimer's disease: from ethnobotany to phytotherapy. J Pharm Pharmacol. 1999;51(5):527-34.

19.Misane I, Ogren SO. Selective 5-HT1A antagonists WAY 100635 and NAD-299 attenuate the impairment of passive avoidance caused by scopolamine in the rat. Neuropsychopharmacology. 2003;28(2):253-64.

20.Ballard CG, Greig NH, Guillozet-Bongaarts AL, Enz A, Darvesh S. Cholinesterases: roles in the brain during health and disease. Curr Alzheimer Res. 2005;2(3):307-18.

21.Bejar C, Wang R-H, Weinstock M. Effect of rivastigmine on scopolamine-induced memory impairment in rats. Eur J Pharmacol. 1999;383(3):231-40.

22.Mallet PE, Beninger RJ, Flesher SN, Jhamandas K, Boegman RJ. Nucleus basalis lesions: Implication of basoamygdaloid cholinergic pathways in memory. Brain Res Bull. 1995;36(1):51-6.

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[DOI: 10.22088/jbums.17.3.51]

23.Bhattacharya SK, Muruganandam AV. Adaptogenic activity of Withania somnifera: an experimental study using a rat model of chronic stress. Pharmacol. Biochem Behav 2003;75(3):547-55.
24.El Sherbiny DA, Khalifa AE, Attia AS, Eldenshary Eel-D. Hypericum perforatum extract demonstrates antioxidant properties against elevated rat brain oxidative status induced by amnestic dose of scopolamine. Pharmacol Biochem Behav. 2003;76(3–4):525-33.
25.Trofimiuk E, Walesiuk A, Braszko JJ. St John's wort (Hypericum perforatum) diminishes cognitive impairment caused by the chronic restraint stress in rats. Pharmacol Res. 2005;51(3):239-46.
26.Saija A, Scalese M, Lanza M, Marzullo D, Bonina F, Castelli F. Flavonoids as antioxidant agents: Importance of their interaction with biomembranes. Free Radic Biol Med. 1995;19(4):481-6.
27.Khalifa AE. Hypericum perforatum as a nootropic drug: enhancement of retrieval memory of a passive avoidance conditioning paradigm in mice. J Ethnopharmacol. 2001;76(1):49-57.
28.Park SJ, Kim DH, Lee IK, Jung WY, Park DH, Kim JM, et al. The ameliorating effect of the extract of the flower of Prunella vulgaris var. lilacina on drug-induced memory impairments in mice. Food Chem Toxicol. 2010;48(6):1671-6.
29.Lamaison JL, Petitjean-Freytet C, Carnat A. Medicinal Lamiaceae with antioxidant properties, a potential source of rosmarinic acid. Pharm Acta Helv. 1991;66(7):185-8.
30.Psotová J, Kolář M, Soušek J, Švagera Z, Vičar J, Ulrichová J. Biological activities of Prunella vulgaris extract. Phytother Res. 2003;17(9):1082-7.
31.Sharma R, Gupta R. Cyperus rotundus extract inhibits acetylcholinesterase activity from animal and plants as well as inhibits germination and seedling growth in wheat and tomato. Life Sci. 2007;80(24–25):2389-92.
32.Rabiei Z, Hojjati M, Rafieian-Kopaeia M, Alibabaei Z. Effect of Cyperus rotundus tubers ethanolic extract on learning and memory in animal model of Alzheimer. Biomed Aging Pathol. 2013;3(4):185-91.
33.Koetter U, Barrett M, Lacher S, Abdelrahman A, Dolnick D. Interactions of Magnolia and Ziziphus extracts with selected central nervous system receptors. J Ethnopharmacol. 2009;124(3):421-5.
34.Chang SC, Hsu BY, Chen BH. Structural characterization of polysaccharides from Zizyphus jujuba and evaluation of antioxidant activity. Int J Biol Macromolec. 2010;47(4):445-53.
35.Zhao J, Li SP, Yang FQ, Li P, Wang YT. Simultaneous determination of saponins and fatty acids in Ziziphus jujuba (Suanzaoren) by high performance liquid chromatography-evaporative light scattering detection and pressurized liquid extraction. J Chromatogr A. 2006;1108(2):188-94.
36.Li LM, Liao X, Peng SL, Ding LS. Chemical Constituents from the Seeds of Ziziphus jujuba var. spinosa (Bunge) Hu. J Integr Plant Biol. 2005;47(4):494-8.
37.Heo HJ, Park YJ, Suh YM, Choi SJ, Kim MJ, Cho HY, et al. Effects of oleamide on choline acetyltransferase and cognitive activities. Biosci Biotechnol Biochem. 2003;67(6):1284-91.
38.Oda Y. Choline acetyltransferase: The structure, distribution and pathologic changes in the central nervous system. Pathol Int. 1999;49(11):921-37.
39.Rabiei Z, Rafieian-kopaei M, Heidarian E, Saghaei E, Mokhtari S. Effects of Zizyphus jujube extract on memory and learning impairment induced by bilateral electric lesions of the nucleus basalis of meynert in rat. Neurochem Res. 2014;39(2):353-60.
40.Omidbaigi R. Production and Processing of Medicinal Plants, 2nd ed. Mashhad:Astane Ghods Publications; 2000. p.106-22. [In Persian]
41.Hosseinzadeh H, Nassiri Asl M.. Anticonvulsant sedative and muscle relaxant effects of carbenoxlone in mice. BMC Pharmacol. 2003;3:1-18.
42.Wang D, Yuan X, Liu T, Liu L, Hu Y, Wang Z, et al. Neuroprotective activity of lavender oil on transient focal cerebral ischemia in mice. Molecules. 2012;17(8):9803-17.
43.Perry N, Court G, Bidet N, Court J, Perry EK. European herbs with cholinergic activities: potential in dementia therapy. Int J Geriatr Psych. 1996;11(12):1063-9.
44.Li J, Wang C, Zhang JH, Cai JM, Cao YP, Sun XJ. Hydrogen-rich saline improves memory function in a rat model of amyloid-beta-induced Alzheimer's disease by reduction of oxidative stress. Brain Res. 2010;1328:152-61.
45.Freeman BA, Crapo JD. Biology of disease: free radicals and tissue injury. Lab Invest. 1982;47:412-26.

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46.Balu M, Sangeetha P, Murali G, Panneerselvam C. Age-related oxidative protein damages in central nervous system of rats: modulatory role of grape seed extract. Int J Dev Neurosci. 2005;23(6):501-7.
47.Muralidharan P, Kumar VR, Balamurugan G. Protective effect of Morinda citrifolia fruits on β-amyloid (25–35) induced cognitive dysfunction in mice: An experimental and biochemical study. Phytother Res. 2010;24(2):252-8.
48.Wang R, Yan H, Tang XC. Progress in studies of huperzine A, a natural cholinesterase inhibitor from Chinese herbal medicine1. Acta Pharmacol Sin. 2006;27(1):1-26.
49.Pachauri SD, Tota S, Khandelwal K, Verma PR, Nath C, Hanif K, et al. Protective effect of fruits of Morinda citrifolia L. on scopolamine induced memory impairment in mice: A behavioral, biochemical and cerebral blood flow study. J Ethnopharmacol. 2012;139(1):34-41.
50.Masuda T, Toi Y, Bando H, Maekawa T, Takeda Y, Yamaguchi H. Structural identification of new curcumin dimers and their contribution to the antioxidant mechanism of curcumin. J Agric Food Chem. 2002;50(9):2524-30.
51. Morovvati H, Najafzadeh H, Azizian H. Evaluation of Effect of Curcumin on Changes of Liver in Adrenalectomised Rats. J Babol Univ Med Sci. 2013;15(3):59-64. [In Persian]
52.Keys JD. Chinese herbs, their botany, chemistry and pharmacodynamics. Rutland,VT: C.E. Tuttle Co.;1976. p.45-9.
53. Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, et al. Curcumin inhibits formation of amyloid β oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J Biol Chem. 2005;280(7):5892-901.

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