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Abstract

Background: There are some factors such as age, stress and emotions that may lead to impaired learning, memory loss, amnesia, and dementia or threats like Schizophrenia and Alzheimer's disease (AD). Traditional Iranian medicine (TIM) recommended some herbs and herbal preparations for treatment or prevention of CNS problems. In this study, the scientific evidences related to effectiveness of TIM herbal medicine on memory and learning will be reviewed.

Materials and Methods: The scientific evidences of the plant efficacy were searched in electronic databases including Pub Med, Scopus, SID, Science Direct, and Google Scholar by keywords like memory, Alzheimer, amnesia, learning and scientific plant names from 1969 to 2014.

Results: The finding of this study confirmed effectiveness of some of TIM medicinal plants on enhancing memory and learning or in treatment or prevention of amnesia and AD. Some of TIM plants like *Melissa officinalis*, *Crocus sativus* and *Nigella sativa* showed improving effect on memory in clinical trials. In some cases, the active principles responsible for efficacy of these plants on memory were also determined.

Conclusion: Most of the studies on TIM plants were designed in animal models and a few herbs were evaluated in clinical trials on AD. Also, for some of the herbal medicine used in TIM, there are no or not enough studies to confirm their effectiveness on memory and learning. Therefore, further experimental and clinical studies are necessary to evaluate the effectiveness of these plants on memory and AD and also to determine the active components of them.

Key words: Memory, Iranian Traditional Medicine, Medicinal plants, learning

Introduction

Learning is the process of acquiring knowledge about the world, and memory is the retention of the acquired knowledge which can be retrieved as and when required (Kupfermann, 1993). Memory is an important part of Cognition for which the brain plays interesting games of neurotransmitter with billion of neurons. Different types of memory are associated with different parts of the brain. For example, Short term memory is associated with prefrontal cortex, Long term memory occurs in hippocampus and temporary lobe and skill memory processed in cerebellum (Terry et al., 2011). The disturbance in such area leads to amnesia and hence memory loss (Soman et al., 2013). Poor learning abilities, impaired memory, lower retention and slow recall are the common problems in stressful situations. Moreover, age, stress and emotions are conditions that may lead to impaired learning, memory loss, amnesia, and dementia or to more ominous threats like Schizophrenia and AD (Francis et al., 1999) AD is a neurodegenerative disease that is characterized by progressive memory loss and cognitive impairment and beta-amyloid (A β) depositions and defects of neural functions (Long and Dougherty, 2003; Selkoe, 1994).

Nowadays, it seems that pharmacotherapy use of psychoactive drugs which are not effective in all cases and exerts numerous side effects (especially with long term administration) causes different problems (Vyawahare et al., 2007). On the other hand, there are some medicinal herbs which recommended through different traditional medicine as memory enhancing agents or treatment of amnesia. Some of these herbs like *Hypericum perforatum*, *Ginkgo biloba* or Ginseng showed significant effect in experimental or clinical studies on memory and learning (Rai et al., 1991; Wesnes et al., 2000; Hasanein and Shahidi, 2011; Abd-Elhady et al., 2013).

Traditional Iranian medicine (TIM) includes all the knowledge and practices used in diagnosis, prevention and elimination in Persia from ancient times to present and its roots go back over 2000 years (Naseri, 2004). TIM has recommended some herbs and herbal preparations for treatment or prevention of CNS problems like epilepsy, Parkinson and amnesia (called Nesyan in TIM). In the previous review, we mentioned the most important plants in TIM for treatment of epilepsy (Abdollahi Fard and Shojaii, 2013). In the present study, the most important herbal medicine mentioned for memory enhancing and treatment of amnesia will be reviewed and also scientific evidences which confirm their effectiveness will be discussed.

Materials and Methods

In this paper, we reviewed the most important ancient herbal treatments which are effective on learning, memory or treatment of amnesia and AD. To find these herbal medicines, the most famous TIM books like Makhzan, Tohfeh, Tebe Akbari, and Moalejate

Aghili were searched and then plant scientific names were identified using combinations of old and new sources. We considered these medicinal herbs as the key words for the next step of our study (Arzani, 2005; Aghili Khorasani, 2009; Tonkaboni, 2007). Then electronic databases including Pub Med, Scopus, SID, Science Direct, and Google Scholar were searched from 1966 to 2014 for each of the plants in TIM plus memory, Alzheimer, amnesia and learning as the keywords; the findings summarized as tables.

Results

There are some medicinal plants which were used in TIM for treatment of "Nesyan" (means amnesia) or for enhancing memory and learning. The results showed that there are some experimental and clinical trials to confirm the effectiveness of these plants on memory and learning and treatment of amnesia or related disease like Alzheimer (Table 1 & 2).

Acorus Calamus

Acorus calamus is recommended for enhancing memory in TIM. Evaluation of the effect of *A. calamus* on improvement of learning and memory showed that oral and intraperitoneal administration of the extract in higher dose could have increase spatial recognition and recalling the data (Naderi et al., 2010). In a study, the effect of a polyherbal formulation (Bramhi Ghrita) containing *A. calamus* on learning and memory in rats was evaluated. This preparation caused significant reduction in transfer latency in Elevated Plus Maze (EPM) and escape latency in Morris Water Maze (MWM) test and so it act as a memory enhancer formulation (Achliya et al., 2004).

The effect of *A. calamus* extract and its active principle, a-asarone on memory impairment, revealed that co-administration of rats with *A. calamus* and a-asarone could prevent the stress induced alterations significantly. So administration of *A. calamus* extract and a-asarone prevent noise; this noise stress induced memory impairment (Sundaramahalingam et al., 2013).

Allium Sativum

Garlic is mentioned to be effective in treatment of amnesia in TIM. Evaluation of the acute and chronic effects of crude garlic extract on learning and memory showed that long-term administration of crude garlic extract may improve learning and memory in mice while the underlying mechanism of action may be attributed to the anti-Acetylcholine Esterase (AChE) activity and anti-oxidant property of garlic (Mukherjee and Banerjee, 2013). Also, it showed that twelve week treatment with shallot or garlic significantly prevented the learning and memory deficits induced by fructose-feeding (Jalal et al., 2011). Evaluation of the mechanism of garlic effect on memory showed that garlic administration in rats affects brain serotonin (5- hydroxytryptamine) levels and memory-enhancing effect of garlic may be due to increase in serotonin metabolism in rat brain (Haider et al., 2008).

Table 1: Traditional medicinal plants for memory and learning

Name of plant	Traditional name	Part used in TIM	Preparation or compound used in experimental study
<i>Acorus calamus</i> (Araceae)	Vaj	Roots	Ethanol extract Ethylacetate extract □-asarone poly herbal formulation
<i>Allium sativum</i> (Alliaceae)	Soom	bulb	Crude garlic Extract Aged garlic extract Cooked garlic extract S-allylcysteine Z-ajoene
<i>Anacyclus pyrethrum</i> (compositae)	Aghargharha	Roots	Hydroalcoholic extract
<i>Boswellia sp.</i> (Burseraceae) <i>B. serrata</i>	Condor	Gum resin	Gum resin aqueous extract Ethanol extract □-boswellic acid
<i>B. papyrifera</i>			aqueous extract Boswellic acid fraction
<i>B. carterii</i>			aqueous Extract Ethylacetate fraction N-butanol fraction
<i>Cocos nucifera</i> Arecaceae	Narjil	Water	Coconut water
<i>Crocus sativus</i>	Za'faran		Alcoholic extract

(Iridaceae)			Methanol/water extract Herbal formulation Crocine safranin
<i>Cyperus rotundus</i> Cyperaceae	So'de Kofi	Roots	Ethanol extract
<i>Ferula asa-foetida</i> (Apiaceae)	Anghoseh	Gum resin	Aqueous extract
<i>Lavandula sp.</i> (Lamiaceae) <i>L. officinalis</i> <i>L. angustifolia</i> <i>L. hybrida</i>	Ostokhodoss	Aerial parts	Ethanol extract Aqueous extract Essential oil Odor(Part of aromatherapy)
<i>Melissa officinalis</i> (Lamiaceae)	Badrangboyeh	Aerial parts	Hydroalcoholic extract Ethanol extract
<i>Nigella sativa</i> (Ranunculaceae)	Shoneez	Seeds	oil
<i>Phyllanthus embelica</i> (Phyllanthaceae)	Amlaj	Fruits	Methanol extract Hydroalcoholic extract
<i>Ruta graveolens</i> (Rutaceae)	Sudab	Aerial parts	Methanol extract
<i>Santalum album</i> (Santalaceae)	Sandal	Wood	Alcoholic extract Aqueous extract
<i>Terminallia chebula</i> (Combretaceae)	Halile-kaboli	Fruits	Seed powder
<i>Teucrium polium</i> (Lamiaceae)	Ja'deh	Aerial parts	Hydroalcoholic extract Aqueous extract
<i>Vitis vinifera</i> (Vitaceae)	Maveez*	Fruits	Methanol extract Methanol fraction Viniferin glucoside Seed polyphenolic extract skin extract of black grape
<i>Zingiber officinalis</i> (Zingiberaceae)	Zangebil	Rhizoms	Alcoholic extract Hydroalcoholic extract Essential oil Zingicomb(ginger+ginkgo)

*Maveez is a dried fruit of some kinds of grape

There are lots of studies about the effect of aged garlic on memory and its mechanism of action. Investigation of the beneficial effects of fresh, aged, and cooked garlic extracts on memory in diabetic rats showed that fresh and cooked but not aged garlic extract (AGE) increased memory in diabetic rats significantly (Sarkaki et al., 2013). Another studies showed that chronic ingestion of this extract markedly improved the learning deficits of Senescence-accelerated mouse (SAM) and also prevented brain atrophy and kept the brain size at the control level (Nishiyama et al., 1997; Moriguchi et al., 1996). AGE also improved learning and memory deficits of SAM and showed an antiaging effect on the SAM (Moriguchi et al., 1997). Chauhan and Sandoval showed that feeding of AGE prevented deterioration of hippocampal based memory tasks in mice and suggesting that AGE has a potential for preventing AD progression (Chauhan and Sandoval, 2007). It was suggested that consumption of garlic may lead to inhibition of A β aggregation and AGE may improve cognitive impairment against A β -induced neuronal deficit, and has a beneficial effects on AD (Gupta et al., 2009; Jeong et al., 2013).

S-allylcysteine is a major thioallyl compound found in garlic extract. Investigations revealed that diet supplementation with S-allylcysteine may reduce age-related learning disabilities and cognitive disorders in senescence-accelerated mice (Nishiyama et al., 2001). Furthermore AGE and its active ingredients, S-allyl-L-cysteine can restrict several pathological cascades related to the synaptic degeneration and neuroinflammatory pathways associated with AD (Ray et al., 2011) and AGE protects neuronal PC12 cells against A β (25-35) toxicity in a dose dependent manner (Griffin et al., 2000).

The inhibitory effects of Z-ajoene, major compound containing sulfur in oil-macerated garlic products, showed against scopolamine-induced memory impairment in mice. This study suggested that Z-ajoene may act on the cholinergic system and on memory impairment caused by excess activity of AChE (Yamada et al., 2004).

Anacyclus Pyrethrum

Anacyclus pyrethrum, called "Aghergherha" in TIM, has been recommended for improving memory in traditional medicine. Pre-treatment with the extract of *A. pyrethrum* roots (250 and 500 mg/kg) showed antiepileptic effect and also showed protection

against cognitive impairment by decreasing oxidative stress and rho kinase ROCK II expression in pentylenetetrazol kindled mice (Pahuja et al., 2013).

Boswellia Sp.

The gum resin of *Boswellia* species (commonly named oilbanum) recommended for enhancing memory and treatment of amnesia in traditional texts. The effect of olibanum gum resin on memory and learning of rat newborns was investigated in numerous studies. In a study by Rasoli et al., aqueous extract of *B. carterii* gum resin (especially in dose 0.05 g/kg) showed significant effect on learning ability and especially in the strengthening and maintaining of memory in rat's newborns comparing to control groups (Tavakkolifar et al., 2009; Rasoli et al., 2001). Also, consumption of oilbanum in lactation period (8 weeks) in female rats has a good effect on learning and short-term memory of newborns which their mothers use of this gum during lactation (Vahidi et al., 2003). Hosseini et al. showed that olibanum could prevent impaired learning and memory caused by methimazole-induced hypothyroidism in adult rats (Hosseini et al., 2010).

Ethyl acetate and N-butanol fractions of *B. carterii* gum resin showed significant effects on enhancing the memory ability in rats which was much significant with ethyl acetate fraction (Hosseinzadeh et al., 2010). Consumption of the aqueous extract of *B. serrata* gum resin in rat mothers during lactation in two-month old rats showed significant increase in short-term memory and long-term memory in experimental group as compared to control group (Hosseini SharisAbad et al., 2003). Evaluation of the effect of the aqueous extract of *B. papyrifera* on learning and memory revealed that it can be an agent for facilitation of learning and memory (Farshchi et al., 2010). Another study on *B. papyrifera* revealed that it can affect spatial memory retention irrespective of the treatment period and also systemic administration of the boswellic acids fraction obtained from *B. papyrifera*, enhanced spatial memory retention in a dose-dependent manner (Mahmoudi et al., 2011).

The dendritic systems are the functional core of neuronal collections as they signify most of the receptive surface of neurons and their organization is essential for integration and transfer of information at the synaptic level (Sharifabad and Esfandiari 2007). In a study using *Boswellia*-treated young rats prenatally, it was concluded that better learning and memory performance in the offspring of the mothers who consumed olibanum during their pregnancy is related to an increase in the somal volume of hippocampal neurons in cornu ammonis and also these rats showed more dendritic branches in CA3 (cornu ammonis) pyramidal neurons (Sharifabad and Esfandiari 2007). Beta boswellic acid, the major component of *Boswellia serrata* gum resin, could enhance neurite outgrowth and branching in hippocampal neurons. Also long-term administration of *Boswellia* resin can attenuate age-related dendritic regression in the superior region of cornu ammonis pyramidal cells in rat hippocampus (Hosseini-Sharifabad and Esfandiari, 2015).

Cocos Nucifera

Cocos nucifera (coconut) is recommended for improving and enhancing memory in TIM. It was reported that young coconut water has a high concentration of a hormone – estrogen - which helps to delay the onset of AD. This experiment on removing both ovaries of white mice, as a model of women with menopause that are deficient in estrogen, revealed that the mice that received the coconut water have less pathological symptoms than the ones that did not receive it. It is stated in her recent study that young coconut water could significantly reverse some pathologies associated with AD (Chomchalow, 2013).

Crocus Sativus

Crocus sativus (Saffron) is an important TIM herb which is mentioned to enhance memory. There are numerous studies about the effect of saffron and its active constituent's crocin, crocetin and safranal on learning, memory and AD. Investigation of the effects of an alcohol extract of *C. sativus* on learning and memory suggested that saffron extract ameliorates the impairment effects of ethanol on learning and memory processes, and possesses a sedative effect (Zhang et al., 1994). In another study showed that pre-training treatment with *C. sativus* extract could significantly antagonized the scopolamine-induced performance deficits in the step-through passive avoidance test (Pitsikas and Sakellaridis, 2006). It has been shown that *C. sativus* extract antagonized ethanol-induced memory impairment in the passive avoidance task in the mouse (Sugiura et al., 1995a).

Evaluation of the effect of saffron in aged mice showed significant improvement in learning and memory in saffron-treated mice, accompanied by reduced lipid peroxidation products, higher total brain antioxidant activity and reduced caspase-3 activity in age groups of mice (Papandreou et al., 2011). Investigation of the cognitive enhancement effect of an herbal extract containing *C. sativus* showed that this preparation can reduce the decline in spatial cognition, which might be due to its effects on reducing A β plaque formation and ameliorating histopathology and ultra structure in hippocampus of mouse brain (Cong et al., 2012).

Crocine is one of the active constituents of saffron which has been reported to enhance memory (Pitsikas et al., 2007). Saffron extract and crocine improved ethanol-induced impairments of learning behaviors in mice, and prevented inhibition of hippocampal long-term potentiation induced by ethanol (Abe and Saito, 2000). Also, it reported that crocine (50 to 200 mg/kg) had beneficial effect on improving of ethanol-induced memory retrieval deficit of mice in passive avoidance task (Sugiura et al., 1995b). Saito showed that crocine improved learning deficits by attenuating the inhibitory effect of ethanol on long-term potentiating generation, and it can be considered as a candidate for treatment of ethanol-induced central nervous system disorders (Saito, 2004). Also, crocine can inhibit scopolamine-induced impairments of spatial learning and memory in rats (Ghadami and Pourmotabbed, 2009). It has been shown that Intracerebroventricular streptozotocin (STZ) can cause cognitive impairment in rats. Evaluation of the effects of crocine on cognitive performance of these rats showed that crocine treatment improved cognitive performance and resulted in a significant reduction in malondialdehyde levels and elevation in total thiol content and glutathione peroxidase activity (Naghizadeh et al., 2013). Further studies revealed that crocine specifically antagonizes the inhibitory effect of ethanol on N-methyl-D-aspartate (NMDA) receptor-mediated responses in hippocampal neurons (Abe et al., 1998). *C. sativus* extract and crocine have potential effect in the treatment of neurodegenerative diseases such as AD (Khalili et al., 2009; Khalili and Hamzeh, 2010).

Also, saffron extract and crocin, improve spatial cognitive abilities following chronic cerebral hypo-perfusion and these effects may be related to the antioxidant effects of these compounds (Hosseinzadeh et al., 2012). Evaluation of the effect of *C. sativus* stigma extract and its constituents, crocin and safranal, on memory and learning showed that saffron aqueous extract, crocin and safranal did not have effect on intact memory but the saffron extract and crocin inhibited the hyoscine unpaired acquisition/performance activity (Hosseinzadeh and Ziaei, 2006). A similar study supported previous findings and suggested crocin involvement in the modulating storage and/or retrieval of information. Crocin also showed positive effects in preventing the impairment of learning and oxidative stress damage induced by chronic stress (Ghadroost et al., 2011).

The effect of saffron on AD was studied in several studies. It was shown that the water: methanolic extract of *C. sativus* stigmas inhibited Ab-peptide fibrillogenesis possibly due to the presence of trans-crocin-4 and its digentibiosyl moiety (Papandreou et al., 2011).

Two clinical trials by Akhondzadeh et al. revealed the effectiveness of saffron in mild to moderate AD (AD). In one study, 46 patients with probable AD received saffron capsules (15 mg) twice daily. Results suggest that using saffron capsules can be associated with a better outcome on cognitive functions compared to the placebo group in a 16-week study (Akhondzadeh et al., 2010a). Another study on 54 adults with similar doses of saffron evaluated the efficacy of saffron compared with donepezil (10 mg/day) in treating mild to moderate AD in a 22-week trial. Results demonstrate similarity in cases with adverse effects except vomiting, which occurred more frequently in the donepezil treated group (Akhondzadeh et al., 2010b). In a randomized double-blind clinical trial, treatment of electroconvulsive therapy-induced memory impairment with a preparation including saffron in patients with mood disorders caused improvement in impaired memory, especially one or two months after the last electroconvulsive therapy session. However, it had no significant effects during and immediately after the electroconvulsive therapy period (Akuchekian et al., 2012). (Table 2)

Cyperus Rotundus

Cyperus rotundus is used for improving of memory in TIM. Evaluation of the effect of ethanolic extract of *Cyperus rotundus* root (100, 200 mg/kg) on midazolam induced acute memory loss revealed that this extract significantly decreases the transfer latency in EPM which measures the increase in memory at the time of retrieval and therefore *Cyperus rotundus* shows significant nootropic activity on retrieval and non significant on consolidation (Soman. et al., 2013).

Also, investigation of the effect of *C. rotundus* tubers on learning and memory in the rat model of AD suggest that *C. rotundus* tubers has some repairing effects on the memory and behavioral disorders produced by lesioning of the nucleus basalis of Meynert in rats (Rabiei et al., 2013).

Ferula Asafoetida

Ferula species are endemic plants of Iran and recommended for nervous problems like epilepsy and amnesia in TIM. Oral administration of *Ferula asafoetida* aqueous gum extract showed significant improvement in memory score at 400 mg/kg dose in passive avoidance model and dose-dependent improvement of transfer latency in EPM model. Also, dose-dependent inhibition of brain cholinesterase and significant improvement in antioxidant levels were also observed. So, Memory enhancing potential of *F. asafoetida* can be attributed to AchE inhibiting and antioxidant properties (Vijayalakshmi et al., 2012).

Lavandula Sp.

Lavender is used in some CNS disease like epilepsy, seizure and amnesia in TIM. Investigation of the effect of *Lavandula officinalis* extract on memory, learning and nociception in rats showed lavender extract at doses 100, 200 and 400 mg/kg improved learning and memory compared to the control group (Rabiei et al., 2014).

Efficacy of Lavender also studied in AD. Soheili et al. showed that aqueous extract of *L. angustifolia* improves the spatial performance of AD in rat. In the next study, they concluded that the lavender extract at the doses of 100 and 200 mg/kg markedly decreased the extent of Ab aggregates which is a major cause of cognitive dysfunction in AD (Soheili et al., 2012). Also, investigating the protein profile of the effects of aqueous extract of *L. angustifolia* on spatial performance of AD in rats showed 80 new proteins that expressed and 104 protein that suppressed in control group which receive 200 mg/kg of lavender (Videira et al., 2013). Chronic exposure to *L. angustifolia* and *L. hybrida* essential oils in rats subjected to scopolamine-induced dementia, showed positive effect on memory formation and reverse spatial memory deficits induced by dysfunction (Hritcu et al., 2012).

Use of lavender essential oil as a part of an aromatherapy in 28 elderly people (17 of whom had AD), showed significant improvement in personal orientation related to cognitive function after therapy. So, this aromatherapy was efficacious therapy for dementia (Jimbo et al., 2009). In a cross-over experiment, lavender or lemon odor improved performance four weeks later in both free recall and recognition of a word list. In the other experimental group of this study to evaluate the effect of these two odor cues in three learning and memory tests it showed that no significant main effect was observed on recall performance as a result of having lemon or lavender at either learning or test. Although lavender had some effect on problem solving, context-dependent retrieval was seen only in free recall and spatial learning (Parker et al., 2001).

Melissa Officinalis

Melissa officinalis (Lemon balm) is mentioned to improve memory and consciousness in TIM. Hydro-alcoholic extract of *M. officinalis* showed no significant effect on learning in MWM task but increases short-term memory in lower dose (25 mg/kg), although, it may have prevention effect on making short-term memory in higher dose (100 mg/kg) (Yosofi et al., 2011) Soodi et al. reported that *M. officinalis* (200 mg/kg) could significantly enhance learning and memory of rats and significantly ameliorate

scopolamine-induced learning deficit. It is suggested that inhibition of AChE activity by *M. officinalis* extract is the at least one of the mechanisms contributed in memory (Soodi et al., 2014).

There are some clinical trials for evaluating the effect of *M. officinalis* on memory. In a controlled trial, the effect of *M. officinalis* extract on patients with mild to moderate AD was investigated. The results showed that patients who received *M. officinalis* extract experienced significant benefits in cognition after 16 weeks of treatment. The findings was emphasized by the improvements seen in both the cognitive subscale of AD assessment scale and clinical dementia rating–sum of the boxes measures in the Melissa group (Akhondzadeh et al., 2003). In another study the acute effects of *M. officinalis* extract was studied on cognition and mood of healthy, young participants at 7-day intervals. The results showed improvement in accuracy of attention with dose 600 mg of *M. officinalis* and time- and dose-specific reductions in both Secondary memory and working memory factors. This study suggests that the ingestion of single doses of *M. officinalis* can modulate both the mood and the cognitive performance of healthy volunteers in a dose- and time-dependent manner (Kennedy et al., 2003; Kennedy et al., 2002).

Nigella Sativa

The seeds of *Nigella sativa* used for enhancing learning and memory in TIM. Evaluation of the effect of *Nigella sativa* oil on the spatial memory performance of rats revealed that there was a significant decrease in the overall mean number of working memory error in the *Nigella* oil-treated group and therefore *N. sativa* oil could enhance the learning and memory abilities of the rats (Sahak et al., 2013).

In a clinical study, the effect of *N. sativa* on memory, attention and cognition in elderly volunteers was evaluated in two groups of volunteers during 9 weeks. The results showed significant difference in the score of logical memory test-I and II, total score of digit span, 30 min delayed-recall, percent score in Rey-Osterrieth complex figure test, time taken to complete letter cancellation test, time taken in trail making test-A and test-B, score in part C of stroop test due to ingestion of *N. sativa* and there were not statistically significant changes in any of the biochemical markers during the study period. So, it can be a good candidate food for preventing alzheimer's disease (Bin Sayeed et al., 2013) (Table. 2)

Phyllanthus Emblica

Phyllanthus emblica or *Embellica officinalis* is recommended for enhancing learning and memory in TIM. Evaluation of the memory enhancing effect of the methanolic extract of *P. emblica* fruits showed that it could significantly improve learning and memory, prevented scopolamine and sodium nitrite induced experimental amnesia and may be a great potential in memory deficits (Ashwlayan and Singh, 2011). In another study it revealed that embellica extract possesses memory enhancing, antioxidant and anti-cholinesterase activity (Golechha et al., 2012). Vasudevan et al. showed that *Anwala churna* (*Embellica officinalis* Gaertn) caused a dose-dependent improvement in memory scores of mice and also it reversed the amnesia induced by scopolamine and diazepam. So it may prove to be a useful remedy for the management of AD (Vasudevan and Parle, 2007).

Ruta Graveolens

Ruta graveolens is mentioned to increase nous in TIM. Evaluation of the efficiency of *R. graveolens* and *Peganum harmala* extract in management of neuroinflammatory insults and neuronal apoptosis characterizing AD showed that treatment of AD-induced rats with these methanolic extract, significantly ameliorates the cholinergic dysfunction and inflammation-induced neurodegeneration characterizing AD. These effects were achieved through the powerful anti-inflammatory activity and anti-apoptotic effects of these extract (Salem et al., 2013).

Santalum Album

Santalum album wood has been suggested for enhancing memory in TIM. In a study by Azmathulla et al., aqueous extract of *S. album* increase the level of acetyl cholinesterase helpful in the brain for storing the memory and so it has a memory enhancing property in mice (Azmathulla et al., 2010). Memory enhancing effect of the alcoholic extract of *S. album* was studied in mice induce with A β protein for memory loss. The results show that the *S. album* has the property of increased enzyme levels. So, *S. album* L. has the memory enhancing property (Papaiah et al., 2010).

Terminallia Chebula

Terminallia chebula has been used for different illnesses in TIM. It is recommended for improving memory and mind and also treatment of amnesia. The ripe fruit of *T. chebula* is regarded as a promoter of intellect and memory, and is believed to prolong life (Manyam, 1999; Misra, 1998). The ripe fruit is reputed to retard the ageing process and to improve cognitive processes and so, has benefits in AD (Manyam, 1999).

In a study by Park et al., oral administration of *T.chebula* seeds (100mg/Kg) for 7 days caused neuroprotective effect against ischemic damage in hippocampal C₁ regions of the gerbil (Park et al., 2011).

Teucrium Polium

Teucrium polium was mentioned to exhibit positive effects on memory in Iranian traditional texts. The cognitive impairment which occurs in diabetes mellitus, in a study by Hasanein and Shahidi, showed that administration of *T.polium* for 30 days from the onset of diabetes improved passive avoidance learning and memory of control rats and alleviated the negative influence of diabetes on learning and memory (Hasanein and Shahidi, 2012). The findings of another study to evaluate anti-amnesic

activity of lamiacea plants including *T. polium* L., *salvia officinalis* and *Melissa officinalis* revealed that *T. polium* was active dose-dependently, in anti-amnesic experiment and it had the highest inhibition in the anticholinesterase assay among other plants (Orhan and Aslan, 2009).

Vitis Vinifera

"Maveez" is a type of dried grape fruits which is mentioned for improving learning in TIM. The effect of methanolic extract of *Vitis vinifera* and methanolic fraction of the extract on memory and behavior mediated by monoamines was studied and the results suggest that *V. vinifera* possess nootropic activity in view of its facilitator effect on retention of learned task (Kakad et al., 2008). Aβ peptides have an important role in AD. In a study by Riviere et al., viniferin glycoside, which was extracted from stem of *V. vinifera*, exhibited the strongest inhibitory activity of Aβ (25-35) aggregation *in vitro*. Also, viniferin glycoside inhibited Aβ cytotoxicity and the non-covalent complex between viniferin glycoside and Aβ (Rivière et al., 2010; Richard et al., 2011).

In another study, administration of grape seed polyphenolic extract for five months inhibits Aβ oligomerization *in vitro* and attenuates cognitive impairment and AD-related neuropathology in the brains of transgenic mice (Liu et al., 2011). The black grape skin extract reduces the reactive oxygen species production, protects the cellular membrane from oxidative damage, and consequently prevents DNA fragmentation and so; it may be used to ameliorate the progression of pathology in AD disease therapy (Russo et al., 2003).

Zingiber Officinale

The rhizomes of *Zingiber officinale* (ginger) were used for improving memory in TIM. Evaluation of the effects of alcoholic extract of ginger in rats showed that cognitive function and neurons density in hippocampus of rats receiving ginger extract were improved while the brain infarct volume was decreased. Indeed, it reduced cognitive deficits induced by focal cerebral ischemia (Wattanathorn et al., 2011).

3, 4-methylenedioxymethamphetamine (MDMA) is known to produce brain damage and spatial memory impairment. Findings of a study by Mehdizadeh et al. revealed that *Z. officinale* could protect brain damage in MDMA treated rats and reduced learning memory deficits that were induced by MDMA (Mehdizadeh et al., 2012). In another study, the essential oil of ginger produced a cognitive impairment, in the passive avoidance test. The effects of ginger essential oil may be dependent on an antagonist action on the central muscarinic cholinergic system (Bezerra Felipe et al., 2008). Evaluation of the effectiveness of *Z. officinale* in combination with *ginkgo biloba* extracts revealed that 1 mg/kg of this mixture improved escape learning in the water maze test (Topic et al., 2002).

Discussion

Poor learning abilities, impaired memory, lower retention and slow recall are the common problems in stressful situations. In addition, age, stress and emotions are conditions that may lead to impaired learning, memory loss, amnesia, and dementia or AD. AD is a neurodegenerative disease and characterized by loss of learning ability with ageing (Francis et al., 1999, Terry et al., 2011).

Herbal medicine has been used for improving learning ability and enhancing memory in different traditional medicines. TIM suggests some plants as single herb or in form of preparations for improving memory and for amnesia (Aghili Khorasani, 2009; Tonkaboni, 2007). In this article, the most important TIM herbal treatments which are effective on learning, memory or treatment of AD and amnesia and also scientific evidences for their efficacy were reviewed.

For Some of these plants, such as saffron, Olibanum gum, Garlic, Lavender and lemon balm, there are several studies which confirmed the memory enhancing ability and effectiveness of them on learning and memory. The efficacy of saffron, lemon balm, lavender and *Nigella sativa* was confirmed in clinical studies too. For some herbs such as saffron, garlic or ginger, the major chemical constituents which may responsible for their memory enhancing effect was also studied.

There are some other herbal medicines in TIM which have still not been investigated for their pharmacological effect on memory, such as *Pistacia vera* (Fostogh), *Pistacia lentiscus* (Mastaki) and *Urginea maritime* (Esghil).

Medicinal herbs which reviewed in this article would be good candidates for future studies on memory or treatment of AD and amnesia. Some of TIM herbs such as *Ruta graveolens* or *Cocos nucifera* need further studies to confirm their effectiveness on memory. It is suggested that more experimental and clinical studies were designed to confirm effectiveness of TIM plants on memory, learning and AD as well as determining their active principles and mechanisms of action.

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Table 2: Clinical studies of TIM medicinal plants effective on memory

Plant name	Design	Intervention	participants	Out come	reference
<i>Crocus sativus</i>	Multi-center, double blind RCT*(22-week)	15 mg cap saffron(twice daily) or Donpezil(5mg twice daily)	54 adults with mild to moderate AD**	Saffron at this dose was effective similar to donepezil	(Akhondzade et al., 2010b)
<i>Crocus sativus</i>	RCT (16week)	15 mg cap saffron(twice daily) or placebo	46 patients with mild to moderate AD	Saffron has significantly better outcome than placebo	(Akhondzadeh et al., 2010a)
<i>Crocus sativus</i>	double blind RCT	Herbal combination(9gr twice daily) or placebo	Mood disorders which candidate for electroconvulsive therapy	Improvement in impaired memory	(Akuchekian et al., 2012)
Lavender	crossover method with washout period 28 days	Part of aromatherapy***	28 elderly people(17 of whom had AD)	significant improvement in personal orientation related to cognitive function	(Jimbo et al., 2009)
Lavender	Cross-over study	Lavender or lemon odor	1****.Ninety first year psychology undergraduates participated	Context-dependent retrieval in free recall and spatial learning	(Parker et al., 2001)
<i>Mellia officinalis</i>	Double blind RCT (4 months)	Mellia extract 60 drops/day or placebo	2. Forty-eight undergraduate subjects	42 patients with mild to moderate AD	significant improvement in cognition in mellisa group
<i>Mellia officinalis</i>	Double-blind RCT, balanced cross over	Single dose of 300, 600, 900 mg of mellisa or placebo	Healthy participants	modulate the mood and the cognitive performance	(Kennedy et al., 2003; Kennedy et al., 2002)
<i>Nigella sativa</i>	RCT (9 weeks)	500 mg cap or placebo	40 Healthy elderly volunteers	significant difference in the score of logical memory test	(Bin Sayeed et al., 2013)

*RCT= Randomized, placebo controlled trial

**AD= Alzheimer's disease

*** aromatherapy contitunts: aroma of 0.04 mL lemon and 0.08 mL rosemary essential oil in the morning and to 0.08 mL lavender and 0.04 mL orange essential oils in the evening

**** Two different experimental groups

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