

Treatment of Alzheimer's Disease in Iranian Traditional Medicine

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Background: Alzheimer's disease (AD) is a progressive neurodegenerative disease with a high prevalence in recent years. Dramatic growth in AD prevalence has increased the importance of more researches on AD treatment. History has shown that traditional medicine can be a source of inspiration to find new therapies.

Objectives: This study tried to codify the recommendations of Iranian traditional medicine (ITM) by studying the main medical manuscripts. The second purpose was to compare these findings with new medical information.

Materials and Methods: Cardinal traditional medical and pharmacological texts from 10th to 18th century were searched for traditional terms of dementia (Nesyan, Fisd-uz-Zekr, Faramooshkari) focused on treatment methods. The findings were classified into three groups: lifestyle recommendations, dietary approaches, and drug therapies. These findings were compared with new medical findings.

Results: ITM has dietary recommendations for dementia such as increasing consumption of nuts, poultry and eggs, milk, and grape products (like raisin and currant). These compounds are full of unsaturated fatty acids, cholesterol, and polyphenolic compounds. New findings suggest that these substances can help in prevention and treatment of AD. ITM has some lifestyle considerations like increasing physical and mental activities, listening to music, attending musical feasts, and smelling specific perfumes. New medical findings confirm nearly all of these recommendations. Along with the aforementioned items, treatment with natural medicines is in the first line of traditional treatment of dementia. New investigations show that many of these herbs have antioxidant, anti-inflammatory factors and acetylcholine esterase inhibitory effects. A few of them also have N-methyl-D-aspartate (NMDA) blocking activity. When these herbs are put together in traditional formulations, they can comprehensively fight against the disease.

Conclusions: More ethnopharmacological and ethnomedical studies on ITM antidementia therapy can be followed by fruitful results.

Keywords: Alzheimer's Disease; Traditional Medicine; Diet; Lifestyle

1. Background

Alzheimer's disease (AD) is a progressive neurodegenerative disease with a great statistical growth in recent years. According to estimations, the number of people with AD dementia is predicted to become nearly triple by 2050 (1). Dramatic increase in AD prevalence has increased the importance of more works on AD treatment. History has shown that traditional medicine can be a source of inspiration to find new therapies (2). Iranian traditional medicine (ITM) is one of the oldest medical schools with more than 1000 years of history (3). Fortunately, there is a kind of dementia in ITM with similar signs and symptoms of AD. ITM explains the causes of diseases by a well-known Greek theory: humorism. In this theory, all body organs have a healthy temperament (Mizaj) which is consisted of a mixture of four fundamental qualities i.e. hotness, coldness, dryness, and wetness (4, 5). When the equilibrium of these

qualities is disturbed, the temperaments of the organs change and they are swerved into unhealthy temperament which is traditionally called "intemperament". For instance, if the temperament of the brain is swerved into coldness, cold intemperament of the brain will occur. Based on this theory, ITM classifies dementia into four subdivisions: simple cold, cold and wet, cold and dry, and hot and dry (6-8). Comparison between signs and symptoms of each kind of traditional dementia with those of AD indicates that there is a strong similarity between "cold and dry" dementia with AD (Table 1). Therefore, antidementia recommendations of ITM could be generalizable to AD.

2. Objectives

In this study, we tried to gather antidementia preven-

tive and therapeutic approaches of ITM including the life style and diet considerations in addition to traditional drug therapy. We studied the compatibility of these recommendations with new medical findings.

3. Materials and Methods

Cardinal traditional medical and pharmacological texts including Al-Hawi (Rhazes, 10th century), Canon of Medicine (Avicenna, 11th century), Zakhira Khawrazmshahi (Jorjani, 12th century), Tohfath-ul-Mo'menin (Mo'men-Tonekaboni), Kholasatul-Hikma and Makhzanul-Advia (Aghili, 18th century), and Exir-e-A'zam (Chisti, 19th century) were searched for traditional terms of dementia (Nesyan, Fisad-uz-Zekr, Faramooshkari) (6-12). The findings were classified into three groups: lifestyle recommendations, dietary approaches, and drug therapies.

4. Results

4.1. Dietary Recommendations

ITM divides edible materials into three types: food, drug, and poison. According to ITM, foods and drinks are of the most important items to keep the body healthy. ITM advises some general points for consumption of foods and drinks:

- 1) Avoiding overeating (6, 9).
- 2) Avoiding consuming one kind of food instead of using different ones (6, 11).
- 3) Avoiding hard physical activities after meals, but stroll after meal is preferred (6).
- 4) Avoiding strong psychological emotions after meals (6).
- 5) Avoiding drinking water with or immediately after meals. Instead, if drinking is inevitable, it is recommended to drink a sherbet containing honey or water extract of agarwood (*Aquilaria* spp.) or mastic (6).
- 6) Adjusting dishes with seasons. In winter, meals should have "hot" temperament, bigger portion and high calorie. It should be also digested slowly (Kathif). In summer, however, meals should have "cold" temperament, small portion and low calorie, and should be digested easily (Latif) (6, 11).

Moreover, ITM has specific dietary recommendations for old people:

- 1) Eating small and multiple meals because stomach becomes weak in the elderly (6).
- 2) Avoiding dense and heavy foods because they produce phlegmatic and melancholic humors (6, 11). Examples for these kinds of foods are aubergine, lentil, cucumber, beef, processed meats (like sausage), some kinds of fish, and salty foods.
- 3) Avoiding eating spicy and pungent foods (6, 11).
- 4) Drinking milk if it is tolerable. The best types of milk for elderlies are goat and donkey milks. Honey milk, ginger milk, and Shirberenj (an Iranian sweet

dish prepared by cooking rice in milk) are also recommended (6).

5) Jams (especially "hot" jams like ginger jam, carrot jam, etc.) are also suggested (6).

Along with its preventive role, ITM also considers diet as a compliment of drug therapy. There is a special diet for people afflicted by dementia (7-9). This diet contains both recommendations and abstentions. Table 2 presents the content of this diet in details.

4.2. Lifestyle Consideration

According to our results, ITM has some lifestyle considerations for people with AD:

- 1) Increasing the brain activities via discussing philosophical sciences, reading, memorizing, and remembering. These activities have been introduced as brain exercises (6, 8, 9).
 - 2) Walking and mild exercises are recommended, but heavy and exhausting exercises are prohibited (6, 9).
 - 3) Sleeplessness especially at night is not allowed, but sleeping a lot, especially in the afternoon with full stomach is also prohibited (6, 9).
 - 4) Overdoing sexual intercourse is forbidden (8, 9).
 - 5) Over-bathing and washing the body with cold or hot water is banned (6, 9).
 - 6) Attending friendly circles and ceremonies, especially music ceremonies are suggested (8).
 - 7) Smelling brain tonic odorous materials including some flowers (like rose, dog rose, jasmine, lily, wallflower, lotus, bitter orange and pussy willow), fruits (like apple), and herbs (like marjoram) are recommended (8).
- Along with dietary advises, these items are prescribed to help the drug therapy of AD.

4.3. Drug Therapy

In ITM, there are two kinds of drugs: singular (Mofrada) and compounded (Morakkaba). Singular drugs consist of one pharmacologically active herb; but in compounded drugs, more than one active herb is involved. Studying the traditional pharmacological manuscripts shows that the number of antidementia singulars has considerably grown from the 10th to the 18th century. While in the 10th century the number of antidementia drugs was 34, this digit reached 130 at the end of the 18th century (440% growth) (Figure 1). This dramatic growth presents a dynamic feature of ITM in drug discovery. Table 3 shows the most prevalent antidementia singulars in details. About compounded drugs, numerous antidementia formulations have been developed during the history of ITM; the most prevalent one is a compound drug named Anaqardia (9). The history of prescription of anaqardia dates back to the Hippocratic era in which this formulation was being used to enhance intelligence, not to treat dementia. Greek physicians were not aware of dementia as a disease, but they considered it as a normal consequence of aging (13, 14).

During the Islamic era, dementia was considered as an independent disease and Anaqardia was allocated to it. The word Anaqardia has been probably arabicized from the Greek word *anacardia*. This name has been assigned to *Semecarpus anacardium* because of the similarity of its fruits to *cardia* (heart) (15). This herb is one of the main constituents of the compound drug, Anaqardia. The other components are: *Terminalia chebula*, *T. belerica*, *Emblica officinalis*, *Nigella sativa*, *Bambusa bambos*, *Elettaria cardamomum*, *Cyperus rotundus*, *Piper nigrum*,

P. longum, *Zingiber officinale*, and *Pimpinella anisum*. All of these herbs are powdered and mixed with honey to make the formulation. Searching the novel pharmacological activities of Anaqardia constituents presented amazing results: eight herbs of 12 have acetyl cholinesterase inhibitory effect; six have anti-inflammatory activity; five are antioxidant; one is N-methyl-D-aspartate (NMDA) antagonistic, and one has anti-beta amyloid production activity (Table 4). It means that this drug attacks AD from different aspects.

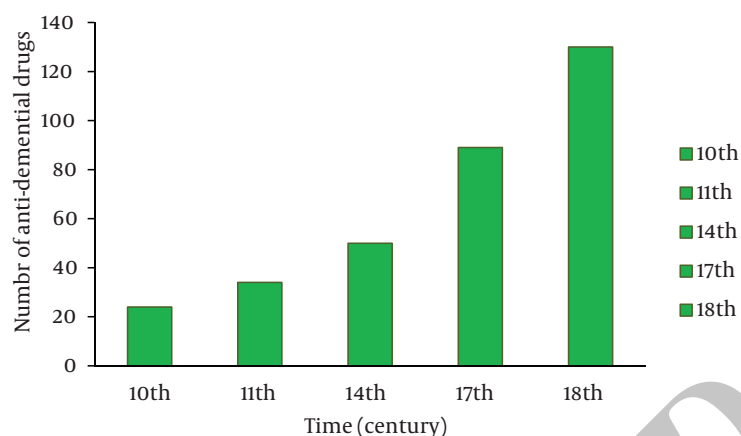
Table 1. Criteria for Diagnosis of Probable Alzheimer's Disease According to NINCDS-ADRDA Alzheimer's Criteria in Comparison With Traditional Signs and Symptoms of Cold and Dry Dementia, Showing Considerable Similarities ^a

Criteria for Diagnosis of Probable Alzheimer's Disease According to NINCDS-ADRDA Alzheimer's Criteria	Signs and Symptoms of Cold and Dry Dementia in ITM
Significant deficiencies in two or more areas of cognition, for example, word comprehension and task completion ability	Difficulty in perception and conception, disremembering recent events while recounting older ones
No loss of consciousness	No loss of consciousness
Onset from ages 40 to 90, typically 65	Prevalence in old ages
No other diseases or disorders that could account for the loss of memory and cognition	Solely resultant of cold and dry intemperament of the brain
Progressive deterioration of specific cognitive functions: language (aphasia), motor skills (apraxia), and perception (agnosia)	Speech impediment, impairment of coordinating complex movements, difficulty in perception and conception
Associated symptoms including depression, insomnia, incontinence, delusions, hallucinations, weight loss, sex problems, and significant verbal, emotional, and physical outbursts	Depression, insomnia
Other neurological abnormalities, especially in advanced disease, including increased muscle tone and a shuffling gait	Muscle stiffness

^a Abbreviations: ITM, Iranian traditional medicine; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association.

Table 2. Traditional Dietary Recommendations and Abstinenances for Dementia (6-9)

	Subgroups
Recommended Food Groups	
Meats	Chicken, sparrow, pheasant, Hoopoe, lark, francolin, lamb
Egg yolks	Goose, quail, turkey, duck, hen
Nuts	Walnut, hazelnut, sweet almond
Fruit products	Raisin, currant, dried fig, coconut
Abstinent Food Groups	
Meats	Goat, beef, rabbit, mutton
Dairy products	Cheese, yogurt
Fruits and vegetables	Melon, squash, lettuce, garlic, onion, cabbage
Legumes and beans	Black bean, kidney bean, cranberry bean, broad bean (immature), lentil

Figure 1. Number of Antidementia Singular Drugs Mentioned in Iranian Traditional Medicine Books From the 10th to the 18th Century

The number of drugs has 440% growth.

Table 3. The Most Prescribed Antidementia Singular Drugs in Iranian Traditional Medicine From the 10th to the 18th Century

Scientific Name	Persian Name	Part Used	Route of Administration/Dosage Form
Herbal			
<i>Acorus calamus L.</i>	Vaj	Rhizome	Oral/decoction
<i>Asperugo procumbens L.</i>	Badranjbuyeh	Aerial part	Nasal, oral/different
<i>Boswelliacarterii Bird</i>	Kondor	Oleogum resin	Oral/syrup
<i>Brassica nigra (L.) Koch</i>	Khardal	Seed oil	Oral/oil
<i>Costus speciosus SM.</i>	Ghost	Rhizome	Topical/lotion
<i>Cyperus rotundus L.</i>	So'd	Tuber	Oral/different
<i>Jasminum officinale L.</i>	Yasamin	Flower	Nasal/perfume
<i>Lavandula angustifolia Mill.</i>	Ostokhoddus	Aerial part	Oral/decoction
<i>Matricaria chamomila L.</i>	Babuneh	Flower	Nasal/inhalant
<i>Nardostachysjatanansi DC.</i>	Sonbol at-Tib	Root	Oral/decoction
<i>Nepeta menthoides Boiss.</i>	Ostokhoddus	Aerial part	Oral/decoction
<i>Nigella sativa L.</i>	Siahdaneh	Seed	Oral/different
<i>Peganumharmala L.</i>	Esfand	Seed	Oral/different
<i>Piper nigrum L.</i>	Filfil-e Siah	Fruit	Oral/Ma'joon
<i>Phyllanthus emblica L.</i>	Amla	Fruit	Oral/Ma'joon
<i>Rosa damascena L.</i>	Gol-e Sorkh	Flower, rosewater, rose oil	Oral/liquid, nasal/perfume, topical/oil
<i>Semecarpus anacardium L.</i>	Belador	Nutshell oil	Oral/oil
<i>Terminali achebula Retz</i>	Halileh	Fruit	Oral/ sachet, jam
<i>Teucrium polium L.</i>	Kalpureh	Aerial part	Oral/decoction
<i>Zingiber officinale Rose</i>	Zanjabil	Rhizome	Oral/jam, Ma'joon
Animal			
<i>Physeterma crocephalus</i>	Anbar	Ambergris	Nasal/inhalant, Oral/different, Topical/oil
<i>Castor Canadensis</i>	Bidastar	Castoreum	Oral, topical
<i>Moschusmos chiferus</i>	Moshk	Musk	Nasal, oral

Table 4. Anaqardia as a Traditional Antidementia Formulation, Probably Inhibiting Alzheimer's Disease Pathology Through All Known Mechanisms (9)^a

Scientific Names	Persian Names	Part Used	Contribution, %	Mechanism of Action			
				AChE Inhibitor	NMDA Blocker	Antioxidant	Anti-inflammatory A β Inhibitor
<i>Terminalia chebula</i>	Halileh-Siah	Fruit	16.7	√			√
<i>Terminalia belerica</i>	Balileh	Fruit	16.7	√		√	
<i>Embelica officinale</i>	Amla	Fruit	16.7	√		√	
<i>Nigella sativa</i>	Siahdaneh	Seed	11	√			√
<i>B. bambos</i>	Tabashir	Bark milk	2.75				√
<i>Eletaria cardamomum</i>	Ghagheleh	Fruit	3.2				√
<i>Cyperus rotundus</i>	So'd	Tuber	2.75	√		√	
<i>Semecarpus anacardium</i>	Belador	Nutshell oil	2.75	√			√
<i>Piper nigrum</i>	Filfil-e Siah	Fruit	5.5	√	√	√	√
<i>Piper longum</i>	Darfilfil	Fruit	5.5		√		√
<i>Piper longum</i>	Darfilfil	Root	5.5		√		√
<i>Zingiber officinale</i>	Zanjabil	Rhizome	5.5	√		√	
<i>Pimpinella anisum</i>	Anisun	Fruit	5.5				

^a Abbreviations: NMDA, N-methyl-D-aspartate; AChE, acetylcholine esterase.

5. Discussion

Traditional medicine is a huge ocean of medical experiments. It contains various treatments for various diseases, each of which can be considered as a clue of finding novel therapeutics. ITM is one of the oldest traditional medicines with more than 1000 years of history. Its precise description of "cold and dry" dementia, it is most probably same as AD. ITM therapeutic prescriptions for AD are classified in three classes: lifestyle modifications, dietary considerations, and drug therapy. In this study, we tried to extract these therapeutic approaches and compare them with new medical findings. Dietary consideration is the first step in ITM-based treatments. ITM considers a group of edibles as functional foods (Ghazā-e-Davāī) (12). These sorts of foods are often prescribed for prevention, but they can also play a role in treatment of diseases as boosters of drugs. As it was shown in the results, grape products (raisin and currant) are one of these functional foods prescribed for dementia. These snacks are full of natural antioxidants including phenolic and polyphenolic substances (16, 17). Recently, it has been revealed that these compounds can act against AD through inhibition of oxidative stress, A β generation and aggregation, and abnormal tau aggregation (18). Nuts including hazelnut, walnut and sweet almond are important parts of ITM antidementia diet. The main constituents of these foods are

unsaturated fatty acids (UFA) (19). Poultry and eggs also have a bold contribution in this diet. These foods are full of cholesterol (19). Concurrent consumption of cholesterol and UFA raises HDL blood level, which has a positive role in AD prevention, according to new studies (19, 20). Traditional lifestyle modifications have been also supported by new findings. There are some studies showing the positive role of cognitive stimulation in prevention of AD cognitive decline (21-23). Cognitive stimulation is often referred to some cognitive tasks (like education, discussion and debate, problem solving and reminiscence), through which attention, memory and other cognitive abilities can be improved. These tasks could be performed socially to help with receiving perceived social support. Cognitive stimulation is partly similar to what are mentioned in ITM as brain exercises. Emphasis on attending friendly circles and ceremonies by ITM may also be efficient in receiving the so-called "perceived social support". Mild physical exercise is also included in the ITM antidementia agenda. Recent studies have substantiated the effects of exercise against AD (24-26). Bending and stretching, slow and brisk walking, calisthenics, rhythmical movements, performing hand movements, and playing with a ball (throwing and kicking) have been shown to improve some of AD consequences (24).

Besides clinical trials, some animal studies have been recently conducted to clarify the therapeutic mechanism of exercise. These researches have demonstrated that exercise can increase cerebral metabolism, perfusion and neurogenesis and may decrease the A β load in the brain of people with AD (24, 27, 28). Another ITM strategy to decrease the dementia outcomes is listening to appropriate music. Recent published studies on effects of music therapy on AD have demonstrated that it can work against AD by increasing the secretion of 17 β -estradiol, testosterone (29) and melatonin (30). Music also reduces agitation and anxiety of patients with AD (31, 32). Smelling brain tonic odors like the scent of some flowers is another traditional antidementia strategy. It is similar to what we know as aromatherapy. Some herbal aromas can improve AD by reducing agitation and inducing neurogenesis (33, 34). In spite of dietary and lifestyle recommendations, the main and the most important traditional method for treatment of dementia is drug therapy. Many singular traditional antidementia drugs can defy AD via blocking the well-known pathological mechanisms. Nearly all the singular antidementia drugs possess antioxidant and anti-inflammatory activities (35-42). Many of these herbs including *A. calamus*, *N. jatamansi*, *N. sativa*, *P. harmala*, *P. longum*, *P. nigrum*, *S. anacardium*, *T. chebula*, and *Z. officinale* show AChEI activities (43-47); and a few of them act through NMDA blockage or A β inhibition (48-50). When these herbs are put together (for example in a formulation), they can comprehensively fight against the disease. Anaqardia is an example of such formulation.

To summarize, ITM recognizes AD as "cold and dry" dementia. It recommends three methods for defeating this disease: diet therapy, lifestyle modification, and drug therapy. In this study, we examined these therapeutic methods by the aid of new medical investigations. Our findings showed that the generality of ITM therapies is in agreement with novel medical information. Therefore, more ethnopharmacological and ethnomedical studies on ITM antidementia therapy can be followed by fruitful results.

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Authors' Contributions

Study concept and design: All the authors. Acquisition of data: Mohammad Mahdi Ahmadian Attari, Meysam Shirzad. Analysis and interpretation of data: Mohammad Mahdi Ahmadian Attari. Drafting of the manuscript: Mohammad Mahdi Ahmadian Attari. Critical revision of the manuscript for important intellectual content: Mahmoud Mosaddegh, Abolhassan Ahmadiani, Leila Dargahi, Mohammad Kamalinejad.

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References

1. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. *Neurology*. 2013;**80**(19):1778-83.
2. Patwardhan B. Ethnopharmacology and drug discovery. *J Ethnopharmacol*. 2005;**100**(1-2):50-2.
3. Emami M, Sadeghpour O, Zarshenas MM. Geriatric management in medieval Persian medicine. *J Midlife Health*. 2013;**4**(4):210-5.
4. Emtiazy M, Keshavarz M, Khodadoost M, Kamalinejad M, Gooshahgir SA, Shahradsajjad H, et al. Relation between Body Humors and Hypercholesterolemia: An Iranian Traditional Medicine Perspective Based on the Teaching of Avicenna. *Iran Red Crescent Med J*. 2012;**14**(3):133-8.
5. Steele R, Singer DW. The Emerald Table. *Proc R Soc Med*. 1928;**21**(3):485-501.
6. Gonzalez CJ. *The canon of medicine of Avicenna*. New York: AMS Press; 1973.
7. Jorjani SE. *Zakhira Khawrazmshahi*. Tehran: Bonyad-e frahange Iran; 1976.
8. Chishti A. *Exir-e Azam 19th century*. Tehran: Research Institute for Islamic and Complementary Medicine; 2004.
9. Rhazes. *[Al-Hawi The Continence]*, translated by Tabatabai. Tehran: Alhavi Pharmaceutical Company; 1990.
10. Mo'men Tonekaboni M. *Tohfah-ul-Mo'menin 11th century*. Tehran: Nashr-e Shahr; 2007.
11. Aghili Khorasani. *Kholasat ul-Hikmah 18th century*. Qom: Esmailian Publication; 2006.
12. Aghili Khorasani. *Makhsan al- Adviah (Collection of Drugs) 18th century*. Tehran: Enqelab-e Islami Publishing and Educational Organization; 1992.
13. Berchtold NC, Cotman CW. Evolution in the conceptualization of dementia and Alzheimer's disease: Greco-Roman period to the 1960s. *Neurobiol Aging*. 1998;**19**(3):173-89.
14. Karenberg A, Forstl H. Dementia in the Greco-Roman world. *J Neurol Sci*. 2006;**244**(1-2):5-9.
15. Al'am H. Balador. In: Haddad-Adel G editor. *Encyclopedia of the world of Islam*. Tehran: Encyclopaedia Islamica Foundation; 1999. pp. 694-7.
16. Williamson G, Carughi A. Polyphenol content and health benefits of raisins. *Nutr Res*. 2010;**30**(8):511-9.
17. Breksa AP, Takeoka GR, Hidalgo MB, Vilches A, Vasse J, Ramming DW. Antioxidant activity and phenolic content of 16 raisin grape (*Vitis vinifera* L.) cultivars and selections. *Food Chem*. 2010;**121**(3):740-5.
18. Pasinetti GM. Novel role of red wine-derived polyphenols in the prevention of Alzheimer's disease dementia and brain pathology: experimental approaches and clinical implications. *Planta Med*. 2012;**78**(15):1614-9.
19. Ahmadian Attari MM, Mosaddegh M, Kazemnejad A, Noorbala AA. Comparison between complementary dietary treatment of Alzheimer disease in Iranian traditional medicine and modern medicine. *Iran J Pub Health*. 2013;**42**(12):1414-21.
20. Siguel E. A new relationship between total/high density lipoprotein cholesterol and polyunsaturated fatty acids. *Lipids*. 1996;**31** Suppl:551-6.
21. Vidovich MR, Shaw J, Flicker L, Almeida OP. Cognitive activity for the treatment of older adults with mild Alzheimer's disease (AD)-PACE AD: study protocol for a randomised controlled trial. *Trials*. 2011;**12**:47.
22. Mapelli D, Di Rosa E, Nocita R, Sava D. Cognitive stimulation in patients with dementia: randomized controlled trial. *Dement Geriatr Cogn Dis Extra*. 2013;**3**(1):263-71.
23. Bahar-Fuchs A, Clare L, Woods B. Cognitive training and cognitive rehabilitation for persons with mild to moderate dementia of the Alzheimer's or vascular type: a review. *Alzheimers Res Ther*.

- 2013;**5**(4):35.
24. Eggermont L, Swaab D, Luiten P, Scherder E. Exercise, cognition and Alzheimer's disease: more is not necessarily better. *Neurosci Biobehav Rev.* 2006;**30**(4):562-75.
 25. Yu F, Kolanowski AM, Strumpf NE, Eslinger PJ. Improving cognition and function through exercise intervention in Alzheimer's disease. *J Nurs Scholarsh.* 2006;**38**(4):358-65.
 26. Perez CA, Cancela Carral JM. Benefits of physical exercise for older adults with Alzheimer's disease. *Geriatr Nurs.* 2008;**29**(6):384-91.
 27. Mustroph ML, Chen S, Desai SC, Cay EB, DeYoung EK, Rhodes JS. Aerobic exercise is the critical variable in an enriched environment that increases hippocampal neurogenesis and water maze learning in male C57BL/6J mice. *Neuroscience.* 2012;**219**:62-71.
 28. Adlard PA, Perreau VM, Pop V, Cotman CW. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. *J Neurosci.* 2005;**25**(17):4217-21.
 29. Fukui H, Arai A, Toyoshima K. Efficacy of music therapy in treatment for the patients with Alzheimer's disease. *Int J Alzheimers Dis.* 2012;**2012**:531646.
 30. Kumar AM, Tims F, Cruess DG, Mintzer MJ, Ironson G, Loewenstein D, et al. Music therapy increases serum melatonin levels in patients with Alzheimer's disease. *Altern Ther Health Med.* 1999;**5**(6):49-57.
 31. Svansdottir HB, Snaedal J. Music therapy in moderate and severe dementia of Alzheimer's type: a case-control study. *Int Psychogeriatr.* 2006;**18**(4):613-21.
 32. Vasionyte I, Madison G. Musical intervention for patients with dementia: a meta-analysis. *J Clin Nurs.* 2013;**22**(9-10):1203-16.
 33. Ballard CG, O'Brien JT, Reichelt K, Perry EK. Aromatherapy as a safe and effective treatment for the management of agitation in severe dementia: the results of a double-blind, placebo-controlled trial with Melissa. *J Clin Psychiatry.* 2002;**63**(7):553-8.
 34. Jimbo D, Kimura Y, Taniguchi M, Inoue M, Urakami K. Effect of aromatherapy on patients with Alzheimer's disease. *Psychogeriatrics.* 2009;**9**(4):173-9.
 35. Manikandan S, Srikumar R, Jeya Parthasarathy N, Sheela Devi R. Protective effect of Acorus calamus LINN on free radical scavengers and lipid peroxidation in discrete regions of brain against noise stress exposed rat. *Biol Pharm Bull.* 2005;**28**(12):2327-30.
 36. Banno N, Akihisa T, Yasukawa K, Tokuda H, Tabata K, Nakamura Y, et al. Anti-inflammatory activities of the triterpene acids from the resin of *Boswellia carteri*. *J Ethnopharmacol.* 2006;**107**(2):249-53.
 37. Srivastava S, Singh P, Jha KK, Mishra G, Srivastava S, Khosa RL. Antiinflammatory, Analgesic and Antipyretic Activities of Aerial Parts of *Costus speciosus* Koen. *Indian J Pharm Sci.* 2013;**75**(1):83-8.
 38. Ramprasath VR, Shanthi P, Sachdanandam P. Anti-inflammatory effect of *Semecarpus anacardium* Linn. Nut extract in acute and chronic inflammatory conditions. *Biol Pharm Bull.* 2004;**27**(12):2028-31.
 39. Ali BH, Blunden G. Pharmacological and toxicological properties of *Nigella sativa*. *Phytother Res.* 2003;**17**(4):299-305.
 40. Hajhashemi V, Ghannadi A, Hajiloo M. Analgesic and Anti-inflammatory Effects of *Rosa damascena* Hydroalcoholic Extract and its Essential Oil in Animal Models. *Iran J Pharm Res.* 2010;**9**(2):163-8.
 41. Tariq M, Ageel AM, al-Yahya MA, Mossa JS, al-Said MS. Anti-inflammatory activity of *Teucrium polium*. *Int J Tissue React.* 1989;**11**(4):185-8.
 42. Meghwal M, Goswami TK. Piper nigrum and piperine: an update. *Phytother Res.* 2013;**27**(8):1121-30.
 43. Gholamhoseinian A, Moradi MN, Sharifi-Far F. Screening the methanol extracts of some Iranian plants for acetylcholinesterase inhibitory activity. *Res Pharm Sci.* 2009;**4**(2):105-12.
 44. Adhami HR, Farsam H, Krenn L. Screening of medicinal plants from Iranian traditional medicine for acetylcholinesterase inhibition. *Phytother Res.* 2011;**25**(8):1148-52.
 45. Ghayur MN, Gilani AH, Ahmed T, Khalid A, Nawaz SA, Agbedahunsi JM, et al. Muscarinic, Ca(++) antagonist and specific butyrylcholinesterase inhibitory activity of dried ginger extract might explain its use in dementia. *J Pharm Pharmacol.* 2008;**60**(10):1375-83.
 46. Kim SJ, Sancheti SA, Sancheti SS, Um BH, Yu SM, Seo SY. Effect of 1,2,3,4,6-penta-O-galloyl-beta-D-glucose on elastase and hyaluronidase activities and its type II collagen expression. *Acta Pol Pharm.* 2010;**67**(2):145-50.
 47. Jukić M, Politeo O, Maksimovic M, Milos M, Milos M. In vitro acetylcholinesterase inhibitory properties of thymol, carvacrol and their derivatives thymoquinone and thymohydroquinone. *Phytother Res.* 2007;**21**(3):259-61.
 48. Xia W, Zeng JP, Chen LB, Jiang AL, Xiang L, Xu J, et al. Inhibition of beta-amyloid precursor protein gene in SK-N-SH cells by piperlonguminine/dihydropiperlonguminine components separated from Chinese herbal medicine *Futokadsura* stem. *Chin J Physiol.* 2007;**50**(4):157-63.
 49. Qi HS, Liu P, Gao SQ, Diao ZY, Yang LL, Xu J, et al. Inhibitory effect of piperlonguminine/ dihydropiperlonguminine on the production of amyloid beta and APP in SK-N-SH cells. *Chin J Physiol.* 2009;**52**(3):160-8.
 50. Hu RQ, Davies JA. Glutamate receptor antagonists reduce spontaneous epileptiform activity in cortical wedges prepared from DBA/2 mice. *Exp Brain Res.* 1997;**115**(2):311-8.