Research Article

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, Fisad-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), Tohfat-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 gout 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 compounddrug, Anaqardia. The other componentsare: *Terminalia chebula*, *T. belerica*, *Emblica officinalis*, *Nigella sativa*, *Bambusa bambos*, *Elettaria cardamomum*, *Cyperusrotundus*, *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 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 Abstinences 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
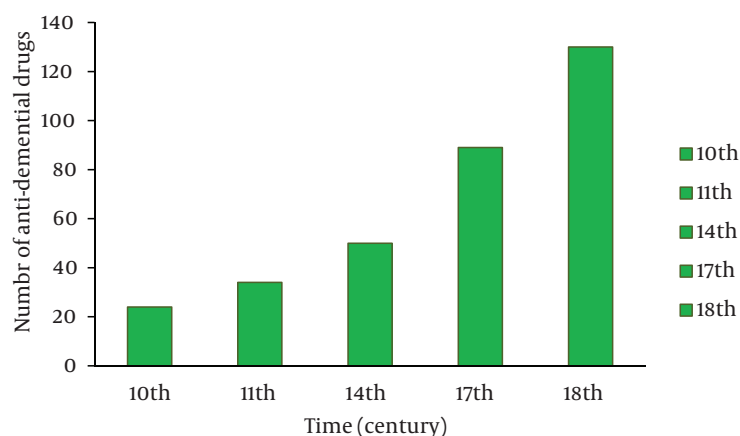
The number of drugs has 440% growth.

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			
Acorus calamus L.	Vaj	Rhizome	Oral/decoction
Asperugo procumbens L.	Badranjbuyeh	Aerial part	Nasal, oral/different
Boswelliacarterii Bird	Kondor	Oleogum resin	Oral/syrup
Brassica nigra (L.) Koch	Khardal	Seed oil	Oral/oil
Costus speciosus SM.	Ghost	Rhizome	Topical/lotion
Cyperus rotundus L.	So'd	Tuber	Oral/different
Jasminum officinale L.	Yasamin	Flower	Nasal/perfume
Lavandula angustifolia Mill.	Ostokhoddus	Aerial part	Oral/decoction
Matricaria chamomila L.	Babuneh	Flower	Nasal/inhalant
Nardostachysjatamansi DC.	Sonbol at-Tib	Root	Oral/decoction
Nepeta menthoides Boiss.	Ostokhoddus	Aerial part	Oral/decoction
Nigella sativa L.	Siahdaneh	Seed	Oral/different
Peganumharmala L.	Esfand	Seed	Oral/different
Piper nigrum L.	Filfil-e Siah	Fruit	Oral/Ma'joon
Phyllanthus emblica L.	Amla	Fruit	Oral/Ma'joon
Rosa damascena L.	Gol-e Sorkh	Flower, rosewater, rose oil	Oral/liquid, nasal/perfume, topical/oil
Semecarpus anacardium L.	Belador	Nutshell oil	Oral/oil
Terminali achebula Retz	Halileh	Fruit	Oral/ sachet, jam
Teucrium polium L.	Kalpureh	Aerial part	Oral/decoction
Zingiber officinale Rose	Zanjabil	Rhizome	Oral/jam, Ma'joon
Animal			
Physeterma crocephalus	Anbar	Ambergris	Nasal/inhalant, Oral/different, Topical/oil
Castor Canadensis	Bidastar	Castoreum	Oral, topical
Moschusmos chiferus	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	Aβ Inhibitor
Terminalia chebula	Halileh-Siah	Fruit	16.7	√			√	
Terminalia belerica	Balileh	Fruit	16.7	√		√		
Embelica officinale	Amla	Fruit	16.7	√		√		
Nigella sativa	Siahdaneh	Seed	11	√			√	
B. bambos	Tabashir	Bark milk	2.75				√	
Eletaria cardamomum	Ghagheleh	Fruit	3.2				√	
Cyperusrotundus	So'd	Tuber	2.75	√		√		
Semecarpus anacardium	Belador	Nutshell oil	2.75	√			√	
Piper nigrum	Filfil-e Siah	Fruit	5.5	√	√	√	√	
Piper longum	Darfilfil	Fruit	5.5		√			√
Piper longum	Darfilfil	Root	5.5		√			√
Zingiber officinale	Zanjabil	Rhizome	5.5	√		√		
Pimpinella anisum	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, Aβ 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 Aβ 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 17β-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 neuropoiesis (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 Aβ 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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