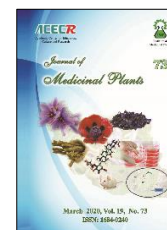




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### Review Article

## Common herbal treatments for senile dementia in ancient civilizations: Greco-Roman, Chinese, Indian, and Iranian

Mohammad Mahdi Ahmadian-Attari<sup>1,2</sup>, Solat Eslami<sup>3</sup>, Leila Dargahi<sup>4</sup>, Ahmad Ali Noorbala<sup>5,\*</sup>

<sup>1</sup> Evidence-based Phytotherapy and Complementary Medicine Research Center, Alborz University of Medical Sciences, Karaj, Iran

<sup>2</sup> Department of Pharmacognosy, Faculty of Pharmacy, Alborz University of Medical Sciences, Karaj, Iran

<sup>3</sup> Dietary Supplements & Probiotic Research Center, Alborz University of Medical Sciences, Karaj, Iran

<sup>4</sup> NeuroBiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>5</sup> Psychosomatic Medicine Research Center, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran

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### ABSTRACT

**Background:** Senile dementia is the most common kind of dementia with considerable social and economic costs. Since the nature of disease is multi-pathological, current treatments cannot cover all aspects of the disease. Recently, scientific considerations have focused on the role of natural products, especially those with traditional backgrounds. **Objective:** to review natural treatments of dementia in ancient Greek, traditional Chinese, Ayurveda, and Iranian traditional medicines with concentration on common herbs concurrently mentioned in two or more than two of them. **Methods:** Scopus database and primary sources were thoroughly searched for selective keywords. The common herbs concurrently mentioned in two or more than two of the aforementioned traditional medicines were selected to deeply investigate for their active ingredients as well as their mechanisms of actions. **Results:** The results showed that *Acorus calamus*, *Nardostachys jatamansi*, *Glycyrrhiza glabra*, *Phyllanthus emblica*, *Semecarpus anacardium*, *Terminalia chebula*, and *Zingiber officinale* had been commonly prescribed for dementia in mentioned traditional systems. According to pharmacological studies, these herbs act their anti-dementia effects via cholinergic, anti-NMDA, antioxidant, anti-inflammatory, anti-apoptotic, and anti- $\beta$  amyloid activities. Furthermore, 16 active principles of these herbs were identified, including  $\alpha$ - and  $\beta$ -asarone, desoxo-narchinol A, narchinol B, glabridin, liquiritigenin, emblicanins A and B, 3, 5, 6, 3', 5', 6'-hexahydroxybiphenyl-2, 2'-dicarboxylic acid, 1',2'-dihydroxy-3'-pentadec-8-enylbenzene, 1',2'-dihydroxy-3'-pentadeca-8,11-dienylbenzene, chebulagic acid, and 1,2,3,4,6-penta-O-galloyl- $\beta$ -D-glucose, Zingipain, 6-gingerol, and 6-shogaol. **Conclusion:** Chinese, Indian, and Iranian traditional medicine can play a complementary and alternative role in preventing and treating senile dementia. The scientific evidence supports their traditional anti-dementia claims.

**Abbreviations:** AChEI, Acetylcholinesterase Inhibitor; AD, Alzheimer's disease; A $\beta$ , Beta amyloid; BuChEI, Butyrylcholinesterase inhibitor; ITM, Iranian traditional medicine; NMDA, N-Methyl-D-aspartic acid; TCM, Traditional Chinese medicine

\* Corresponding author: [noorbala@tums.ac.ir](mailto:noorbala@tums.ac.ir)

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## 1. Introduction

Senile dementia is a general term including a variety of diseases e.g. Alzheimer disease (AD). AD is the most prevalent kind of dementia and is a progressive neurodegenerative disease of the elderly with age being a major risk factor [1]. Improvements in health care in recent years have led to longer life expectancy and perpetual rise of the population average age; therefore, the prevalence of AD is projected to increase over the coming years. Certain recent studies suggest that the sufferers of AD dementia are expected to triple in number between 2010 and 2050 [2]. The cost of providing care for a sufferer of AD in the United States is approximately US\$57,000 per year [3]. These data suggest the need to find either prevention or treatment for AD.

In recent decades, researches have clarified, to some extent, the AD pathology. First, investigations were concentrated on neurotransmitter dysfunctions; “Cholinergic deficit theory” came out of those efforts and led to Acetylcholine esterase inhibitors (AChEIs) like Tacrin, Rivastigmin, Donepezil, and Galantamin [4]. NMDA blockers were also found in the same circumstances. Memantin is the only member of this group which was approved by FDA in 2003 for moderate to severe AD [5]. Both the aforementioned treatments provide temporary and modest improvement in cognitive impairment without affecting the disease drastically [6].

More recently, the “Amyloid Cascade hypothesis” as a new hypothesis emphasizes the impact of amyloid plaques on the pathology of AD [7, 8]. According to this hypothesis, there is an increased production or decreased clearance of beta amyloid (A $\beta$ ) in the brains of AD patients [6]. This hypothesis suggested that the mismetabolism of amyloid precursor protein (APP) is the initiating event in AD pathogenesis,

which results in the aggregation of A $\beta$ , specifically A $\beta$ 42. Formation of neurotic plaques would result in other pathological events such as inflammatory responses, free radical formation, oxidative stress, formation of neurofibrillary tangles (NFTs), disruption of synaptic connections which would result in decreased neurotransmitters, death of tangle-bearing neurons, and dementia [8]. To examine this hypothesis, numerous clinical trials, in order to decrease A $\beta$  production or increase A $\beta$  clearance, have been conducted recently, yet only some of them have shown mild benefit [9]. Following the failure of “Amyloid Cascade hypothesis” to cover all aspects of the disease, a new hypothesis has been more recently developed in which A $\beta$  deposition be explained as an effect rather than the cause of AD [10, 11]. Nowadays, AD is considered a multi-pathological disease and therefore, simple theories cannot cover all aspects of the disease. This complexity needs therapies with multi-target characteristics and natural products –with wide variety of compounds- may be appropriate candidates for investigating anti-AD treatments.

Natural medicines have a long history of use worldwide. Continuous use of natural products for prevention and treatment of different diseases and also as food flavors serves these agents as safe and effective therapies which can be a topic of drug discovery.

## 2. Methods

To investigate the most common natural products prescribed traditionally for AD, Scopus database was thoroughly searched (from beginning to 2018) for these keywords: (Alzheimer’s disease) or (senile dementia) or (dementia) or (forgetfulness) + (traditional Chinese medicine) or (Ayurveda) or (Iranian traditional medicine) or (Persian medicine) or

(ancient medicine) or (Greek traditional medicine). Because of the scientific dominance of the authors on Greek and Iranian traditional medicines, anti-demential natural products of these two civilizations were also searched in primary sources (original traditional medical manuscripts).

After extracting the traditional common treatments, new scientific evidences on the activities of these treatments on pathophysiology of AD as well as the active pharmaceutical ingredients of them were also search in Scopus.

### 3. Results

In this study, we first review the concept of senile dementia in Greco-Roman, Chinese, Indian, and Iranian traditional medicine. Then, we review natural treatments of dementia in these traditional medical schools with concentration on common herbs concurrently mentioned in two or more than two of them. Based on new findings, the probable mechanisms of action of these traditional herbs are also discussed.

#### 3.1. Senile dementia in history

##### 3.1.1. Dementia in Greco-Roman era

Although AD was distinguished from the general term “dementia” in 1907 by a German physician Alois Alzheimer for the first time [12], it is obvious that it has been existed as long as the history of human beings. Pythagoras (7th century B.C), a Greek philosopher, was one of the firsts who was mentioned dementia in his compilations [13]. He presumed ages more than 63 as senium or old ages. He was aware of mental decline in the elderly, but he did not consider it an abnormality, but rather, an inevitable consequence of aging, because aging itself was accompanied by changes in the balance of body fluids that rendered the body cold and dry [13].

Plato and his student Aristotle (384 – 322 B.C.) both mentioned mental failure in the elderly as inseparable outcome of aging. Aristotle never assumes any scenario for old age problems without including mental decline. Beyond this, in spite of important contributions, Aristotle assumed the heart as the source of life and the seat of human intelligence. The brain—bloodless, cold, and without sensation was considered merely a "steaming gland there to cool the heart" [13, 14].

It may be surprising that mental degradation is never mentioned in Hippocratic writings. There are indeed several indications of senile diseases, but debilitation of mental powers, however, is not listed [14].

Galen (150-200 A.D) was the first who identified dementia in senium as a mental – not a heart disease. However, like predecessors, he considered dementia as an unavoidable consequence of old age [13, 14].

Erroneous understanding of dementia may be rooted in rarity of aging population in that time. Estimations show that people with the age 60 were not more than 5 percent of the population. This estimation is less than 3 percent for people who reached 65. Greek physicians did not separate dementia etiologically. The above-mentioned mental deterioration were undoubtedly due to different causes including infections of central nervous system, depression, vitamin deficiency, and cerebral infarcts in addition to the disorder that is currently identified as the Alzheimer disease [14].

##### 3.1.2. Dementia in traditional Chinese medicine (TCM)

Dementia has been partly described in Traditional Chinese Medicine (TCM). Huangdi Neijing (also known as the Yellow Emperor's Inner Canon) is one of the most important books

of TCM and has an important influence on doctrines of Chinese medicine [15]. This book was written 2000 years ago and is composed of two texts in the form of a dialogue between the mythical Huangdi (Yellow Emperor) and six of his fabled ministers. In the first text, Suwen, dementia is mechanistically discussed. As an important TCM concept, Qi is a flowing energy in the body and the essential substance which maintains various physiological activities. Changes of Qi are thought to involve in the pathological process of diseases. In Suwen, the loss of memory was attributed to Qi moving in the wrong direction, as well as the insufficiency of Qi [15]. In the second text of Huangdi Neijing, Lingshu, there is a description about an 80-year-old man, his “soul departed” and his words was irrelevant and confused, because of the insufficiency of Qi in the lungs [15]. Dementia has been also discussed in subsequent TCM books.

Sun Simiao (AD 581–682), the famous Chinese physician also gave an explanation of dementia in his book *Qian Jin Yi Fang* (Supplement to the Formulas of a Thousand Gold Worth) [15]. He wrote, “The people exceeded 50 years old were prone to forgetful, which is attributed to the insufficiency of Qi in the kidney.” [15].

Zhang Jingyue (AD 1563–1640) in his book, *Jing Yue Quan Shu* systematically explained the pathogenesis and therapy of dementia for the first time [15]. He stated that the primary cause of dementia was Qi in the visceral organs moving in the wrong direction, which led to the decreased production of phlegm. He also prescribed a way to overcome this decrease [15].

The first description of the brain as a seat of idea and memory was explained by Wang Qingren (AD 1768–1831). He was an anatomist and for the first time, he found brain atrophy in a

dementia patient. He connected this atrophy with insufficiency of Qi in the brain [15].

### 3.1.3. *Dementia in Indian traditional medicine, Ayurveda*

Ayurveda (life knowledge) is an Indian native traditional system of medicine with a 6500 years history [16]. It is divided into 8 divisions; one of them is Rasayana tantra [17]. Literally, Rasayana means the augmentation of Rasa, the vital fluid produced by the digestion of food. Rasa flows in the body and sustains life. Thus, Rasayana is a method of treatment through which the Rasa is maintained in the body. Charaka Samhita, one of the two important Ayurvedic texts defines Rasayana as promotive treatment to attain longevity, intelligence, freedom from senile disorders, youthful appearance, optimum strength of physique and sense organs, maintenance of language ability, and memory improvement [17, 18]. Rasayana, indeed, is a method of body rejuvenation and therefore, Rasayana drugs are supposed to have memory enhancement activity. Therefore, Rasayana prescriptions are more preventive rather than curative and should be begun in midlife, not too late in old age [16].

### 3.1.4. *Dementia in Iranian traditional medicine (ITM)*

Islam was appeared in Arabia in 610 A.D., spreading rapidly with many people of many regions converting to it by 750 A.D. At that time, Islamic territory included Arabia, Persia, central Asia, Syria, Turkey, north and horn of Africa, and even Hispania in Europe [19]. In this wide territory, different cultures and civilizations mixed together and the Islamic civilization was built. One of the most important parts of Islamic civilization is related to Persia. Persian scientists had a critical role in construction and development of Islamic

civilization and many physicians like Rhazes, Avicenna, Jorjani, Rabban al-Tabari, etc. were Iranian.

Ancient Greek medicine had a strong influence on Iranian traditional medicine (ITM). Thus, the main theory of ITM was humorism. According to the humoral theory, body fluids are consisted of Blood (hot and moist), Phlegm (cold and moist), Yellow bile (hot and dry), and Black bile (cold and dry). When these four cardinal fluids are in equilibrium, the body will be in health; and when this balance is disturbed, sickness will be occurred [20]. During one-thousand-year life of ITM, humoral theory remained almost intact and was the basis of explanation of human pathophysiology [21]. The important role of Iranian physicians was to develop and categorize the diagnosis and treatment of diseases and dementia is no exception.

Regarding the above, Greek medicine supposed dementia as an unavoidable consequence of elderly, not as an independent disease. Except Galen, others were explaining heart as a place of conception and thinking. In this condition, Iranian physicians categorized dementia using their own intellect as well as previous findings.

Ali ibn Sahl Rabban al-Tabari (775–864 A.D.) is the first who produced an encyclopedia of medicine in Islamic era [22]. His book, *Firdous ul-Hikmah* (Paradise of Wisdom) was consisted of 7 sections and 30 parts, with 360 chapters in total. Although most of the book has been written on the basis of Greek sciences, influences of other systems of medicine, especially Indian medicine, are apparent [22]. A very brief chapter of this book has been assigned to dementia. According to etiologies, the author divided dementia into two subgroups: cold and wet, and cold and dry. He also explained different drugs for each kind.

Razi (better known as Rhazes in west) (865-925 A.D.), a prominent Iranian philosopher, alchemist, and physician had also some notes on dementia. In his large comprehensive book, *Al-Hawi*, he gathered medical topics of Greek, Persian, Syriac, Arabic, and Indian origins along with his own critical opinions. In the first volume of this book, he dedicated a chapter to dementia. Razi divided dementia into three divisions according to Galen: dementia caused by simple cold, cold and wet, and cold and dry dys temperament of the brain [23]. Among repeated Greek theories, however, there are some new matters; one of them is the opinion of Serapion Junior (Syriac physician of ninth century who worked in Jundishapur hospital) about the specific part of the brain responsible for memory: “When the temperament of posterior ventricle of the brain is altered, memory will impair. If this impairment is due to [coldness and] moisture, disease will be accompanied with drowsiness, excessive sleeping, hypersalivation, and rhinorrhea; and if the impairment is caused by coldness and dryness, the signs and symptoms will be vice versa.” [23]. Many Persian and Arabic formulation for treatment of dementia have been also presented in this chapter.

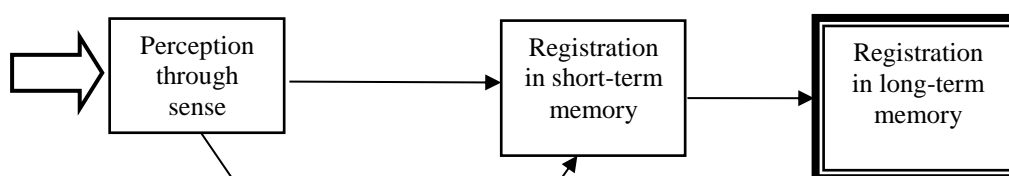
Ibn Sina (Avicenna) (980–1037 A.D.) in his famous book, *Canon of Medicine*, gathered and classified all aspects of medical sciences of his time. He extended the brief and diffused Greek concept of mental disorders to extended, classified, and clarified chapters. Based on traditional anatomy, he referred dementia to 3 different parts of the brain: anterior, middle, and posterior ventricles. Anterior ventricle is responsible for imagination, middle ventricle is the place of thought and judgment, and posterior ventricle is for store of memory [24]. Impairment of each section results in memory impairment: Impaired imagination or thought will result in

registration of wrong things in memory, and memory impairment will result in incorrect registration of even corrected data. This concept was developed as “the brain information flow” in next centuries. Aghili Khorasani (18<sup>th</sup> century) has described this concept properly (Fig. 1) [25]. Despite observation in all of the three conditions, loss of memory is considered as an independent disease only when the posterior ventricle is affected by dystemperament. This disease is called Nesyan (forgetfulness) or Fisad ul-Zekr (deterioration of memory). In other two, memory impairment is assumed as a sign of two other diseases.

One of the most complete descriptions of dementia was made in the eighteenth century by an Indian-Persian physician Hakim Mohammad Azam Khan Chishti in his comprehensive book *Exir-e Azam* (Great Elixir) [26]. According to symptomatology, he described a differential diagnosis for Nesyan. Previous classifications showed dementia could be divided into three subdivisions (see above), but Chishti divided it into five. His precise descriptions make us able to compare his descriptive diseases with today’s illnesses. Table 1 show that there are similarities between cold and dry Nesyan and Alzheimer’s disease.

### 3.2. Traditional treatment of dementia

During Greco-Roman period, dementia was not considered as a disease, and therefore, there were no treatments presented as anti- dementia. Dioscorides (40-90 AD), a Greek physician, pharmacologist, and botanist hints no drugs for dementia or any disorders contributed to memory in his famous book “*De Materia Medica*”. The only herb which is introduced as rejuvenator is balsamum [27]. However, TCM, Ayurveda, and ITM identified dementia as a disease, and therefore, mentioned several herbs for prevention and treatments of dementia. These therapies are divided into 4 categories: drugs prescribed 1) to treat dementia (forgetfulness); 2) to prevent aging and aging consequences; 3) to invigorate the brain and improve memory consolidation; and 4) to clean brain from bad humors responsible for dementia. The most prevalent drugs commonly prescribed for dementia in each aforementioned traditional medicine are presented in table 2. Considerably, seven of these drugs are common among the three medical cultures: *Acorus calamus*, *Nardostachys jatamansi*, *Glycyrrhiza glabra*, *Phyllanthus emblica*, *Semencarpus anacardium*, *Terminalia chebula*, and *Zingiber officinale*.



**Fig. 1.** The brain information flow in Iranian medical texts which was developed by Aghili Khorasani, a Persian-Indian physician and pharmacist of 18<sup>th</sup> century.

**Table 1.** Criteria for diagnosis of probable Alzheimer’s disease according to NINCDS-ADRDA in comparison with traditional signs and symptoms of cold and dry dementia shows considerable similarities.

Criteria for diagnosis of probable Alzheimer's disease according to NINCDS-ADRDA	Signs and symptoms of cold and dry dementia in Iranian Traditional Medicine (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 age 40 to 90, typically 65	Prevalence in old age
No other disease or disorders that could account for the loss of memory and cognition	Solely resultant of cold and dry dystemperament 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

**Table 2.** Single natural compounds traditionally used for treatment of dementia in Chinese, Indian, and Iranian traditional medicines

Scientific name	Traditional name	Traditional source	Traditional mode of action	Reference
<i>Acorus calamus</i>	Chang Pu Vacha Vaj	TCM Ayurveda ITM	Anti-dementia, Anti-aging Memory improvement Brain invigoration	17,23,29,30,31,32
<i>Acorus tatarinowii</i> , <i>A. graminus</i>	Shi Chang Pu	TCM	Memory improvement, Anti-dementia	29,62
<i>Akebia quinata</i> <i>Clematis spp.</i>	Mu tong	TCM	Anti-dementia	29
<i>Alternanthera sessilis</i>	Matyakshika	Ayurveda	Anti-aging	17
<i>Amber</i>	Hu po	TCM	Memory improvement	30
<i>Anemone coronaria</i>	Shaghayegh-e No'man	ITM	Brain purification	23,31,32,49
<i>Angelica sinensis</i>	Dang Gui	TCM	Memory improvement	30,62
<i>Aquilaria agallocha</i>	Oud	ITM	Brain invigoration	31,32,49
<i>Aranea ventricosa</i>	Zhi zhu (wang)	TCM	Anti-dementia	29
<i>Arisaema heterophyllum</i> or other <i>Arisaema spp</i>	Dan nan xing	TCM	Memory improvement	30
<i>Asparagus cochinchinensis</i>	Tian dong	TCM	Memory improvement	30
<i>Astragalus membranaceus var.</i> <i>mongholicus</i>	Huang qi	TCM	Memory improvement	30

**Table 2.** Single natural compounds traditionally used for treatment of dementia in Chinese, Indian, and Iranian traditional medicines (Continue)

Scientific name	Traditional name	Traditional source	Traditional mode of action	Reference
<i>Atractylodes macrocephala</i>	Bai zhu	TCM	Memory improvement	30
<i>Aucklandia lappa</i>	Mu xiang	TCM	Memory improvement	30
<i>Bacopa monnieri</i>	Aindri/Brahmi	Ayurveda	Anti-aging	17
<i>Baliospermum montanum</i>	Chatra (Danti)	Ayurveda	Anti-aging	17
<i>Benincasa hispida</i>	Kushmand	Ayurveda	Anti-aging	17
<i>Biota orientalis</i>	Bai zi ren	TCM	Anti-dementia Memory improvement	29,30
<i>Boerhaavia diffusa</i>	Punarnava	Ayurveda	Anti-aging	17
<i>Boswellia carterii</i>	Kondor	ITM	Anti-dementia, Brain invigoration, Brain purification	31,32,49
<i>Bovinae</i> subfamily	Niu huang	TCM	Anti-dementia	29
<i>Bovinae</i> subfamily	Niu xin	TCM	Anti-dementia	29
<i>Brassica nigra</i>	Khardal	ITM	Anti-dementia, Memory improvement	23,31,32,49,86
<i>Castor fiber</i>	Gond-e Bidastar	ITM	Anti-dementia	23,31,32,49
<i>Celastrus paniculata</i>	Jyotismati	Ayurveda	Anti-aging	17
<i>Centele asiatica</i>	Mandukparni	Ayurveda	Anti-aging	17
<i>Chelidonium majus</i>	Mamiran	ITM	Brain purification	23,31,32,49
<i>Chiroptera</i> order	Fu yi nao	TCM	Anti-dementia	29
<i>Cinnamomum cassia</i> or other <i>Cinnamomum. spp.</i>	Rou gui/Gui zhi	TCM	Memory improvement	30
<i>Citrus aurantium</i>	Zhi shi	TCM	Memory improvement	30
<i>Citrus reticulata</i> <i>C. tangerine</i>	Chen pi	TCM	Memory improvement	30
<i>Coelogyne evalis</i>	Jivanti	Ayurveda	Anti-aging	17
<i>Commiphora mukul</i>	Guggulu	Ayurveda	Anti-aging	17
<i>Convolvulus pluricaulis</i>	Shankhpushpi	Ayurveda	Anti-aging	17
<i>Coptis chinensis</i>	Huang lian	TCM	Anti-dementia	29
<i>Cornus officinalis</i>	Shan zhu yu	TCM	Memory improvement	30
<i>Costus speciosus</i>	Qost	ITM	Anti-dementia, Brain invigoration	23,32,49
$Cu_3(CO_3)_2(OH)_2$	Kong qing	TCM	Anti-dementia, Anti- aging	29
<i>Curculigo orchoides</i>	Xian mao	TCM	Memory improvement	29
<i>Cyperus rotundus</i>	So'd	ITM	Memory improvement	23,31,32,49
<i>Desmodium gangeticum</i>	Sthira (Salaparni)	Ayurveda	Anti-aging	17
<i>Dimocarpus longan</i>	Long yan rou	TCM	Anti-dementia, Memory improvement	29,30



**Table 2.** Single natural compounds traditionally used for treatment of dementia in Chinese, Indian, and Iranian traditional medicines (Continue)

Scientific name	Traditional name	Traditional source	Traditional mode of action	Reference
<i>Dioscorea spp.</i>	Shan yao/ Shu yu	TCM	Anti-dementia	29
<i>Embelia ribes</i>	Vidanga	Ayurveda	Anti-aging	17
<i>Epimedium spp.</i> <i>Ganoderma spp.</i>	Yin yang huo/ Ling zhi/ Chi zhi	TCM	Anti-dementia, Anti-aging	29
<i>Equus ferus</i>	Ma xin	TCM	Anti-dementia	29
<i>Euphorbia adenochlora</i>	Lu' ru	TCM	Anti-dementia	29
Fe(C <sub>2</sub> H <sub>3</sub> O <sub>2</sub> ) <sub>2</sub>	Tie (hua) fen	TCM	Anti-dementia	29
Fossilized bones/teeth	Long gu/chi	TCM	Memory improvement	30
<i>Gentiana scabra</i>	Long dan (cao)	TCM	Anti-dementia, Anti-aging	29
<i>Glycyrrhiza inflata</i> <i>Glycyrrhiza uralensis</i> <i>Glycyrrhiza grabra</i>	Gan Cao Yashtimadha	TCM Ayurveda	Memory improvement Anti-aging	17,29,30,62
<i>Jasminum officinale</i>	Yasamin	ITM	Anti-dementia, Brain invigoration	31,32,86
<i>Lycium chinense</i> <i>L. barbarum</i>	Di gu pi	TCM	Memory improvement	30
<i>Matricaria chamomilla</i>	Baboonaj	ITM	Brain invigoration	31,32,49
<i>mercuric sulfide</i>	Zhu sha	TCM	Memory improvement	30
<i>Moschus spp.</i>	Moshk	ITM	Anti-dementia, Brain invigoration	23,31,32,49
Na <sub>2</sub> SO <sub>4</sub>	Xuan ming fen	TCM	Anti-dementia, Anti-aging	29
<i>Nardostachys jatamansi</i>	Jatamansi Sonbol ut-Tib	Ayurveda ITM	Anti-aging Brain invigoration	17,31,32,49
<i>Nepeta menthoides</i>	Ostokhoddoos	ITM	Anti-dementia, Brain invigoration, Brain purification	31,32
<i>Ophiopogon japonicus</i> <i>O. bodinieri</i>	Mai Dong	TCM	Memory improvement	30,62
<i>Paeonia lactiflora</i>	Bai shao	TCM	Memory improvement	30
<i>Panax ginseng</i>	Ren Shen	TCM	Memory improvement, Anti-dementia, Anti-aging	29,30,62

**Table 2.** Single natural compounds traditionally used for treatment of dementia in Chinese, Indian, and Iranian traditional medicines (Continue)

Scientific name	Traditional name	Traditional source	Traditional mode of action	Reference
<i>Peganum harmala</i>	Esfand	ITM	Anti-dementia, Brain purification	31,32,49
<i>Phyllanthus emblica</i>	Aamla	Ayurveda ITM	Anti-aging Anti-dementia, Memory improvement	17,32,49
<i>Phyllostachys nigra</i>	Zhu li	TCM	Anti-dementia	29
<i>Physeter macrocephalus</i>	Anbar	ITM	Brain invigoration	23,31,49
<i>Phytolacca acinosa</i>	Shang lu (hua)	TCM	Anti-dementia	29
<i>Pinus massoniana</i>	Fu shen mu/ Huang	TCM	Anti-dementia	29
<i>P. densiflora</i>	song jie	TCM	Anti-dementia	29
<i>Piper nigrum</i>	Filfil-e Siah	ITM	Memory improvement	31,32,49
<i>Pollia japonica</i>	Du ruo	TCM	Anti-dementia	29
<i>Polygala tenuifolia</i>	Yuan Zhi	TCM	Memory improvement, Anti-dementia, Anti-aging	29,30,62
<i>Polygonatum verticillatum</i>	Meda (Mahameda)	Ayurveda	Anti-aging	17
<i>Poria cocos</i>	Fu Ling/ Fu Shen	TCM	Anti-aging, Memory improvement	29,30,62
<i>Prunus persica</i>	Tao zhi	TCM	Anti-dementia	29
<i>Psoralea corylifolia</i>	Bakuchi	Ayurveda	Anti-aging	17
<i>Pueraria tuberosa</i>	Vadari	Ayurveda	Anti-aging	17
<i>Punica granatum</i>	Dadim	Ayurveda	Anti-aging	17
<i>Rehmannia glutinosa</i>	Shu Di Huang	TCM	Memory improvement	62
<i>Rosa damascena</i>	Gol-e Sorkh	ITM	Brain invigoration	31,32,49
<i>Salvia miltiorrhiza</i>	Dan shen	TCM	Anti-dementia	29
<i>Saposhnikovia divaricata</i>	Fang feng	TCM	Memory improvement	30
<i>Schisandra chinensis</i> or other <i>Schisandra</i> spp	Wu wei zi	TCM		30
<i>Scrophularia ningpoensis</i>	Xuan shen	TCM		30
<i>Semecarpus anacardium</i>	Bhallataka Belador	Ayurveda ITM	Anti-aging Anti-dementia, Memory improvement	17,23,31,32,49,86
<i>Sida spinosa</i>	Nagabala	Ayurveda	Anti-aging	17
<i>Sinapsis alba</i>	Bai jie zi	TCM	Memory improvement	30
<i>Sphaeranthus indicus</i>	Mundi	Ayurveda	Anti-aging	17

**Table 2.** Single natural compounds traditionally used for treatment of dementia in Chinese, Indian, and Iranian traditional medicines (Continue)

Scientific name	Traditional name	Traditional source	Traditional mode of action	Reference
<i>Terminalia chebula</i>	Haritaki Halila Zard	Ayurveda ITM	Anti-aging	17,23,31,32,49
<i>Testudinidae</i> family	Bie zhua	TCM	Anti-dementia	29
<i>Tetrapanax papyferus</i>	Tong cao	TCM	Anti-dementia	29
<i>Teucrium polium</i>	Ja'da	ITM	Anti-dementia	31,32
<i>Tinospora cordifolia</i>	Guduchi	Ayurveda	Anti-aging	17
<i>Withania somnifera</i>	Ashwagandha	Ayurveda	Anti-aging	17
<i>Zataria multiflora</i>	Sa'tar	ITM	Brain purification, Memory improvement	31,32
<i>Zingiber officinale</i>	Sheng Jiang	TCM ITM	Memory improvement	23,31,32,49, 54
<i>Ziziphus jujube</i> <i>var. spinosa</i>	Suan Zao Ren	TCM	Anti-aging, Memory improvement	29,30,62

### 3.2.1. *Acorus calamus*

Sweet flag (Chinese name: Chang pu; Indian name: Vacha, Persian name: Vaj) is dried rhizomes of a perennial herb, *Acorus calamus*, (Acoraceae family). Recent studies have shown that rhizomes of Sweet flag contain sugar, fatty acids, and some pharmaceutical active ingredients like  $\alpha$ - and  $\beta$ -asarone (Fig. 2) [28].

History of use of Sweet flag in traditional medicines is considerably long. In TCM, Sweet flag has been used for forgetfulness and aging [29, 30]. Ayurveda has utilized this herb as a rejuvenator [17]; and it has been prescribed in ITM for memory improvement and as a brain purifier [23, 31, 32]. Concurrency of use in China, India, and Islamic territory in a long period of time (from 2<sup>nd</sup> to 19<sup>th</sup> century) among genetically different people of this extensive area from Far East to Gibraltar for the same purpose i.e. dementia makes *A. calamus* important enough for more animal and clinical investigations.

Animal behavioral studies have shown the effectiveness of Sweet flag on memory.

Manikadan and colleagues in 2013 showed that extraction of Sweet flag attenuates memory impairment of noise stress. They also revealed that noise stress increases Acetylcholinesterase (AChE) activity, lipid peroxidation, and heat shock protein 70 (hsp70) in hippocampus of rats and *A. calamus* can reduce these consequences. They linked this activity with  $\alpha$ -asarone [33]. It should be noted that AChEI activity of Sweet flag extract had been previously described in 2007 by Oh et al. [34].

Pharmacological activities of  $\alpha$ -asarone against AD pathophysiology have been also investigated. Manikadan and colleagues in two separate studies showed that  $\alpha$ -asarone has anti-oxidant activity [35, 36]. Cho (2002) showed blocking activity of  $\alpha$ -asarone on N-Methyl-D-aspartic acid (NMDA) receptor [37]. A recent study conducted by Hong Ju Lee and Byung Tae Choi showed that  $\alpha$ -asarone significantly promotes proliferation of neural progenitor cells in the dentate gyrus of the hippocampus at 30  $\mu$ M concentration. They also showed that  $\alpha$ -asarone

could promote neural progenitor cells differentiation into neuroblasts [38].

About  $\beta$ -asarone, there are evidences on anti-apoptotic and anti-autophagy effects of this compound [39, 40].  $\beta$ -asarone had also protective effect on beta amyloid toxicity on PC12 cells [41] and in APP/PS1 double transgenic mouse model [42]. Mukherjee and colleagues (2007) pointed out that  $\beta$ -asarone has AChE inhibitory activity [43]. They showed  $IC_{50}$  of both  $\alpha$ - and  $\beta$ -asarone for this activity as 46.38 and 3.33  $\mu$ M, respectively clarifying the predominance of AChE inhibitory activity of  $\beta$ -asarone. Minzhen Deng and coworkers showed that  $\beta$ -asarone administration can improve the learning and memory abilities of APP/PS1 transgenic mice through inhibiting Beclin-1-dependent autophagy by the PI3K/Akt/mTOR signaling pathway. The authors demonstrated that  $\beta$ -asarone lowered AChE and A $\beta$ 2 levels, up-regulated p-mTOR and p62 expression, down-regulated p-Akt, Beclin-1, and LC3B expression, lowered the number of autophagosomes and reduced APP mRNA and Beclin-1 mRNA levels compared with the untreated group [40].

Another study indicated that  $\beta$ -asarone could increase the neuronal survival and decrease the accumulation of A $\beta$  deposits in APP/PS1Tg mice brain. Importantly,  $\beta$ -asarone significantly decreased the expression of the receptor of advanced glycation end products (RAGE) [44].

Wenguang Chang and Junfang Teng demonstrated that  $\beta$ -asarone in combination with tenuigenin could improve the efficacy of memantine in treating moderate-to-severe AD. Moreover, they found that the male AD patients aged 60–74 years with moderate disease might be the most likely candidates to benefit from this novel method [45].

Acute and sub-acute toxicological tests of oral hydroalcoholic extract of Sweet flag showed it is

safe [46]. However, there are evidences of carcinogenicity of Sweet flag essential oil with particular reference to  $\beta$ -asarone [47].

### 3.2.2. *Nardostachys jatamansi*

Spikenard (Indian name: Jatamansi; Persian name: Sonbol ut-Teeb) is dried rhizomes of a perennial herb, *Nardostachys jatamansi* (Valerianaceae), and is endemic to India, Nepal, China and Bhutan [48]. It is used in Ayurveda as a Rasayana drug and therefore, is prescribed in Indian traditional medicine as a rejuvenator [17]. Spikenard has been also continuously used as brain invigorating agent in ITM for more than 700 years [31, 32, 49]. The main constituents of the rhizomes are sesquiterpenes (like Jatamansone) and cumarins (Fig. 2) [48].

Behavioral studies have shown that spikenard can improve learning and memory. There are some evidences which showed ethanolic or methanolic extracts of spikenard can attenuate memory impairment induced by different interventions like chronic stress, sleep deprivation, and scopolamine injection [50-52].

Two separate screening of Indian medicinal plants showed that *N. jatamansi* has AChE inhibitory activity; one of these articles utilized ethanolic extract [53] and another used water fraction of methanolic extract of the herb [54]. Their results showed that water fraction has more AChEI activity with  $IC_{50}$  of 47.21  $\mu$ g/ml [54].

Antioxidant activity of spikenard has been also clarified through some investigations. Sharma and Singh (2012) revealed antioxidant activity of hydroalcoholic extract of spikenard by various antioxidant assays including DPPH, superoxidases, hydroxyl radicals, and NO scavenger activity. They showed that spikenard is a powerful radical scavenger and also has a moderate effect on NO [55]. Dhuna and colleagues (2013) showed cytoprotective effect

of *N. jatamansi* methanolic extract against H<sub>2</sub>O<sub>2</sub> in in vitro culture of C6 glioma cells through increase in antioxidant enzymes. They also pointed out that *N. jatamansi* has reductive effect on lipid peroxidation and expression of stress marker, HSP70 [56].

Recently, more focused studies on anti-AD activities of *N. jatamansi* have been done. Liu and colleagues in 2018 showed that *N. jatamansi* root extract and one of its major component, chlorogenic acid, have a neuroprotective effect against A $\beta$  toxicity in in vitro (A $\beta$ -induced cell death in SH-SY5Y cells) and in vivo (*Drosophila* AD model). They suggested that this neuroprotective activity is related to antioxidant, anti-inflammatory, and extracellular-signal-regulated kinase (ERK) signaling inhibitory action of the extract and its major compound [57].

About active compounds, a Korean team in 2018 published articles about anti-neuroinflammatory effects of two terpenoids desoxo-narchinol A and narchinol B. They showed that these compounds act through inhibiting the production of PGE<sub>2</sub>, iNOS, COX-2 proteins, and pro-inflammatory cytokines, such as IL-1b, IL-6, and TNF-a, in LPS-stimulated BV2 and primary microglial cells [58]. They also showed in a separate study that desoxo-narchinol A and narchinol B can inhibit NF- $\kappa$ B pathway and activate Nrf2/HO-1 pathway by increased phosphorylation of p38 and ERK. They showed that PI3K/AKT signaling has also a role in the activation of HO-1 by these two herbal components. They also revealed that desoxo-narchinol A and narchinol B also increased the phosphorylation of GSK3 $\beta$  at serine-9 residue, following phosphorylation of AKT [59].

### 3.2.3. *Glycyrrhiza glabra*

Licorice (Chinese name: Gan Cao; Indian name: Yashtimadha) is dried rhizomes and roots of a perennial herb, *Glycyrrhiza glabra* (Leguminosae), that is native to the Mediterranean region, central to southern Russia, and Asia Minor to Iran [60]. Ancient therapeutic effects of licorice are mostly gastrointestinal [61] but alongside this activity, it has been prescribed for memory improvement and also as anti-aging in TCM and Ayurveda, respectively [17, 29, 62].

Studies have shown that licorice and one of its major flavonoids, glabridin inhibit memory impairments in scopolamine model of amnesia [63, 64]. This effect may be related to facilitation of cholinergic transmission in brain. Sharifzadeh and colleagues (2008) revealed that memory enhancement of oral administration of licorice water extract is comparable with hippocampal injection of nicotine [65]. Hasanein (2011) showed that glabridin can also reverse learning and memory deficits of diabetic rats [66]. Dhingra and colleagues in 2006 revealed that oral administration of water extract of licorice significantly decreased the activity of AChE enzyme in the brain of Swiss albino mice [67]. Therefore, positive effects of licorice on learning and memory can partly be attributed to cholinergic effects. Anti-apoptotic and neuroprotective activities of glabridin were also pointed out in an ischemic model of brain injury of rat [68].

Along with glabridin, another flavonoid of licorice, liquiritigenin, has been shown to have anti-AD properties (Fig. 2). Lui and colleagues in a series of investigations showed that liquiritigenin has positive effects on behavioral performance of A $\beta$ -injected and transgenic mouse model of AD measured by Morris water maze and shuttle box test [69, 70]. They revealed that liquiritigenin promotes the generation of neurons by decreasing mRNA levels of Notch-2,

an important molecule regulating neuronal proliferation and differentiation [69, 70]. Prior to the aforementioned studies, Lie et al. in 2009 had shown that liquiritigenin increases cell viability, decreases reactive oxygen species (ROS) and apoptosis in *in vitro* cultures of rat hippocampal neurons treated with A $\beta$  25-35 [71].

On the other side, another active ingredient of licorice, carbenoxolone, seems to decrease the learning performances of rats in a spatial memory task. Hosseinzadeh and colleagues (2005) showed that carbenoxolone as a gap-junction channel blocker affect the integrity of the hippocampus and decelerates the learning performances of rats in a spatial memory task [72].

#### 3.2.4. *Phyllanthus emblica*

Indian gooseberry (Indian name: Amla; Persian name: Amlaj) is fruits of a deciduous tree *Phyllanthus emblica* (Syn: *Emblica officinalis*) (Phyllanthaceae) which is native to India, Pakistan, Uzbekistan, Sri Lanka, South East Asia, China, and Malaysia [73]. Ayurvedic texts advices Indian gooseberry to prevent aging but in ITM, it is prescribed either for prevention or treatment of forgetfulness [17, 32, 44]. Investigations have shown that *Phyllanthus emblica* is full of tannoid antioxidants including emblicanin A (37%), emblicanin B (33%), punigluconin (12%) and pedunculagin (14%) [74]. Pozharitskaya and colleagues (2007) showed that radical scavenging activity of emblicanins A and B was 7.86 and 11.20 times more than that of ascorbic acid and 1.25 and 1.78 times more than gallic acid, accordingly [75]. In another study, Bhattacharya and colleagues perturbed radical scavenging enzymes of rat brain by chronic foot shock stress. They showed that tannoids of *Phyllanthus emblica* can normalize the activities of these enzymes

including superoxide dismutase, catalase, and glutathione peroxide [76].

A study conducted by Keo and colleagues (2012) revealed the role of fruit extract of *Phyllanthus emblica* against glutamate-induced cell damage [77]. This study showed that this extract can significantly protect cultured HT22 cells, an immortal mouse hippocampal cell line, against damage and degeneration of glutamate.

In addition to above mentioned researches, there are some behavioral studies on the effect of *P. emblica* on scopolamine induced amnesia [78-80]. Ashwlayan and Singh (2011) published the positive effect of *Phyllanthus emblica* methanolic extract on the performance of scopolamine and nitrite treated mice which had been measured by Morris water maze [79]. In another study, Golechna and colleagues (2012) revealed that hydroalcoholic extract of the fruits of emblica reverses the amnesia, ameliorates the oxidative stress, and reduces the rise of AChE level in the brain of mice induced by scopolamine [80]. Shahab Uddin and Al Mamun demonstrates that ethanolic extracts of *Phyllanthus emblica* fruits showed marked beneficial effects to improve learning and memory. Among ripe and unripe fruits, significant cognitive enhancing effects were observed by unripe fruit which is comparable with the standard [81].

In a study conducted by Justin Thenmozhi et al., administration of tannoid principles of *Phyllanthus emblica* orally to aluminum chloride (AlCl<sub>3</sub>) induced Alzheimer's disease (AD) in rats for 60 days significantly reversed the aluminum concentration, AChE activity, and A-beta synthesis-related molecules in the studied brain regions. Additionally, the extract attenuated significantly the spatial learning, memory, and locomotor impairments observed in AlCl<sub>3</sub> treated rats [82].

Ibraheem Husain et al. showed that tannoid fraction of *P. emblica* reverses the changes in the biomarkers of oxidative stress induced by high salt and cholesterol diet (HSCD) in rats. This tannoid fraction also improved the performance of HSCD rats in Morris water maze task. Additionally, TUNEL assay indicated that *P. emblica* tannoid fraction supplementation led to reversal of DNA fragmentation and apoptosis caused by HSCD. Immunohistochemical analysis and western blotting also showed a surge in the nuclear location of Nrf2 and revealed a novel mechanism of action for this herbal fraction via the Nrf2–ARE pathway [83].

In another study, fractionation of methanolic extract of *P. emblica* by column chromatography showed that 3, 5, 6,3',5', 6'-hexahydroxybiphenyl-2, 2'-dicarboxylic acid is the main effective compound that improves significantly memory deficits in male albino mice induced by scopolamine hydrochloride and sodium nitrite (Fig. 2) [84].

### 3.2.5. *Semencarpus anacardium*

Marking nut (Indian name: Bhallataka; Persian name: Belador) is fruits of a deciduous tree *Semencarpus anacardium* (Anacardiaceae), and is native to sub-Himalayan region, tropical and central parts of India [85]. In Ayurveda, a decoction of marking nut with milk and purified butter was used as a nervine tonic and as a rejuvenator [17, 85]. The preparation of marking nut in ITM is different with Ayurveda. In ITM, resinous content of the fruit which is called traditionally Asal-e Belador (marking nut honey) was used for memory improvement and also treatment of forgetfulness [23, 31, 32, 49, 86].

Milk extract of *Semencarpus anacardium* contains flavonoids, carbohydrates, and traces of phenolic compounds. Behavioral tests showed that Milk extract of *Semencarpus anacardium*

has nootropic effect according to passive avoidance paradigm. On the other hand, this extract has no significant effect on scopolamine- and diazepam-induced amnesia [87].

From another standpoint, marking nut honey, as it was prepared in ITM, has AChE inhibitory effect. Adhami and colleagues (2011) showed that both methanolic and dichloromethane extract of fruit resin have AChE inhibitory activity [88]. Adhami and colleagues (2012) determined IC<sub>50</sub> of dichloromethane extract as 24.12 µg/ml [89]. They also identified active compounds of this total extract as catechol alkenyls with the structures as 1',2'-dihydroxy-3'-pentadec-8-enylbenzene and 1',2'-dihydroxy-3'-pentadeca-8,11-dienylbenzene (Fig. 2). Their IC<sub>50</sub> values on AChE inhibition were 12 and 34 µg/ml, respectively, while they had no butyrylcholinesterase inhibitory (BuChEI).

Previously, AChE inhibitory of stem bark of *Semencarpus anacardium* was also determined. IC<sub>50</sub> of methanolic extract of the stem bark is 16.74 µg/ml, according to Vinutha and colleagues (2007) [54].

Alcoholic extract of marking nut is also neuroprotective. In a study conducted by Bhatnagar and colleagues (2005), they showed that oral administration of alcoholic extract of the herb dissolved in butter can protect hippocampal neurons against chronic immobilization stress [90]. They also exhibited that the herb affects and elevates antioxidant enzymes like superoxide dismutase and catalase. As a marker of oxidative stress, Malondialdehyde was measured and was showed that the extract can significantly decrease this parameter in comparison with stress group.

### 3.2.6. *Terminalia chebula*

Yellow myrobalan (Indian name: Haritaki; Persian name: Halilaj Zard) is fruits of a deciduous tree, *Terminalia chebula*

(Combretaceae), which is native to India, Nepal, south west China, Sri Lanka, Malaysia and Vietnam [91]. It is opulent of phenolic compounds such as gallic acid, ellagic acid, casuarinin, chebulanin, chebulagic acid, chebulinic acid, and 1,2,3,4,6-penta-O-galloyl- $\beta$ -d-glucose [92]. *In vitro* assays have showed that nearly all of these phenolic compounds possess antioxidant effect including anti-lipid peroxidation, anti-superoxide radical formation, and free radical scavenging activities [93, 94]. In a study which has been conducted on PC12 cells, water and also methanolic extracts of *Terminalia chebula* inhibited pernicious effects of H<sub>2</sub>O<sub>2</sub> via antioxidant activity [95]. Furthermore, *Terminalia chebula* has been shown to slowdown the telomere shortening rate by inhibition of oxidative stress [96]. It means that it may have a preventing effect on aging.

An investigation has shown that chebulagic acid isolated from *T. chebula* has dual inhibitory effect on COX and lipoxygenase (LOX) [97]. New researches have shown that dual inhibition of COX and LOX could provide a new therapeutic way for the treatment of aging-related brain disorders such as Alzheimer's disease and neuronal excitotoxicity [98-100].

Moreover, another phenolic constituent from *T. chebula*, 1,2,3,4,6-penta-O-galloyl- $\beta$ -d-glucose (Fig. 2), showed strong AChE and BuChE inhibitory activities with IC<sub>50</sub> values of  $29.9 \pm 0.3 \mu\text{M}$  and  $27.6 \pm 0.2 \mu\text{M}$ , respectively [101].

A behavioral test conducted on normal rats has reported cognitive enhancement of *Terminalia chebula*. In this study, rats who orally received 40 mg/kg water extract of *Terminalia chebula* for two weeks exhibited a significant cognitive enhancement via Morris water maze in comparison with naïve and sham groups [102].

### 3.2.7. *Zingiber officinale*

Ginger (Chinese name: Sheng Jiang; Persian name: Zanjabil) is fresh or dried rhizomes of the plant *Zingiber officinale* (Zingiberaceae). It is widely cultivated in subtropical areas like India. In TCM and ITM, ginger has been used as memory enhancer [17, 23, 31, 32, 49].

Antioxidant and anti-inflammatory effects of ginger have been well documented [103]. Dual inhibition of COX and LOX enhances anti-inflammatory activity of this herb and makes it a good candidate for AD investigations [103] (see section 3.6).

Some articles have reported AChEI and BuChEI activity of ginger. Ghayur and colleagues (2008) showed ginger methanolic extract has BuChEI activity with IC<sub>50</sub> of 0.18 mg/ml [104]. They showed that this effect is mainly related to 6-gingerol. Oboh and colleagues (2012) revealed AChE inhibitory of water extract of ginger with IC<sub>50</sub> of 2.86 mg/ml [105]. Zingipain is a ginger cysteine protease that has been introduced by Rungsaeng et al. (2013) as a AChE inhibitor with K<sub>i</sub> value of 9.31 mg/ml [106].

Ginger has been shown to modulate neuroinflammation induced by microglia activation. Grzanna and colleagues (2004) activated THP-1 cells, a human monocytic cell line with properties similar to human microglial cells, by lipopolysaccharide, proinflammatory cytokines, and fibrillar amyloid peptide A $\beta$  (1-42) to study whether ginger extract can dampen this activation or not [107]. The results documented that the extract inhibits LPS, cytokine, and A $\beta$ -induced expression of the proinflammatory genes TNF- $\alpha$ , IL-1 $\beta$ , COX-2, MIP-alpha, MCP-1, and IP-10. The data provide experimental evidence that ginger can inhibit the activation of human monocytic THP-1 cells by different proinflammatory stimuli and reduce the



expression of a wide range of inflammation-related genes in these microglial-like cells. Ha and colleagues (2012) exhibited that this activity can be related to 6-shogaol [108]. They stimulated BV<sub>2</sub> microglial cell by LPS and revealed that 6-shogaol inhibits the release of NO, the expression of inducible nitric oxide synthase (iNOS), and the production of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and proinflammatory cytokines like IL-1 $\beta$  and TNF- $\alpha$ , and downregulates COX-2, MAPK, and NF- $\kappa$ B expression.

Furthermore, ginger has been shown to attenuate A $\beta$  toxicity *in vitro* and *in vivo*. Kim and colleagues (2007) used methanolic and chloroform extract of ginger to protect PC12 cells from toxicity of A $\beta$  (1-42) [109]. They showed that chloroform extract has stronger activity than methanolic one with EC<sub>50</sub> of 18  $\mu$ g/ml. In another study, SH-SY5Y neuroblastoma cells was treated with A $\beta$  (25-35) and 6-gingerol was evaluated for its protective activity [110]. The results showed that 6-gingerol increases cell viability, decreases apoptosis, reduces peroxide levels caused by ROS and nitrosative stress mediated by NO. 6-gingerol also up-regulates cellular antioxidant defense capacity via activation of Nrf2. In an *in vivo* test, Zeng et al. (2013) used combination of intracerebroventricular injection of A $\beta$  and continuous gavage of AlCl<sub>3</sub> to induce a model of AD in rats [111]. They showed that ginger extract reverses the memory dysfunction induced by this model.

Considerable experimental and animal documents about the effectiveness of ginger on memory dysfunctions (as mentioned above) resulted in a clinical study on middle-aged healthy women [112]. In this study, dried ethanolic extract of ginger containing 7.33% w/w of 6-gingerol and 1.34% w/w of 6-shogaol was used. Women in three equal groups of 20 persons

(served as receivers of placebo, 400, and 800 mg extract daily for 2 months) were evaluated for working memory and cognitive function using computerized battery tests and the auditory oddball paradigm of event-related potentials at three different time periods i.e. before receiving the intervention, one month, and two months. The results of this study showed that 800 mg/day of ginger extract could improve working memory in all domains including power of attention, continuity of attention or accuracy of attention, speed of memory, and quality of memory.

#### 4. Conclusion

Dementia is a repeatedly mentioned and well-known disease in Chinese, Indian, and Iranian traditional systems of medicine. These traditional schools had considered some therapies for prevention and treatment of dementia. In this study, we extracted the common anti-demential herbs from these traditional medicines and presented them as *Acorus calamus*, *Nardostachys jatamansi*, *Glycyrrhiza glabra*, *Phyllanthus emblica*, *Semencarpus anacardium*, *Terminalia chebula*, and *Zingiber officinale*. Using herbs in different medical systems for one therapeutic purpose means that these herbs have therapeutic effects on people with different genetic, environmental, and ethnic or cultural backgrounds; therefore, it makes their therapeutic activities generalizable. Sixty three pharmacological studies indicated that these seven herbs can elicit memory-improving effects via multiple mechanisms of action, covering cholinergic, anti-NMDA, antioxidant, anti-inflammatory, anti-apoptotic, and anti-A $\beta$  activities. These mechanisms are in well accordance with modern pharmacotherapy of AD by prescribing AChE Inhibitors, NMDA blocking agent, anti-inflammatory drugs, antioxidants, and nootropics depending on

different situations. Only one clinical trial studied the activity of one of these herbs, *Zingiber officinale*, on memory. Hence, clinical investigations on these herbs are strongly recommended.

Meanwhile, 16 active molecules were identified including  $\alpha$ - and  $\beta$ -asarone (which are found in *A. calamus*), desoxo-narchinol A and narchinol B (in *N. jatamansi*), glabridin and liquiritigenin (in *G. glabra*), emblicanins A and B, and 3, 5, 6, 3', 5', 6'-hexahydroxybiphenyl-2, 2'-dicarboxylic acid (in *P. emblica*), 1',2'-dihydroxy-3'-pentadec-8-enylbenzene and 1',2'-dihydroxy-3'-pentadeca-8,11-dienylbenzene (in *S. anacardium*), chebulagic acid and 1,2,3,4,6-penta-O-galloyl- $\beta$ -d-glucose (in *T. chebula*), and Zingipain, 6-gingerol, and 6-shogaol (in *Z. officinale*) (Fig. 2). These 16 compounds can serve as active markers for characterization and standardization of corresponding herbs and can also be used in drug discovery as lead compounds.

Taken together, it is concluded that Chinese, Indian, and Iranian traditional medicine can have a complementary and alternative role in preventing and treating senile dementia. The scientific evidence supports their traditional anti-dementia treatments.

#### Author contributions

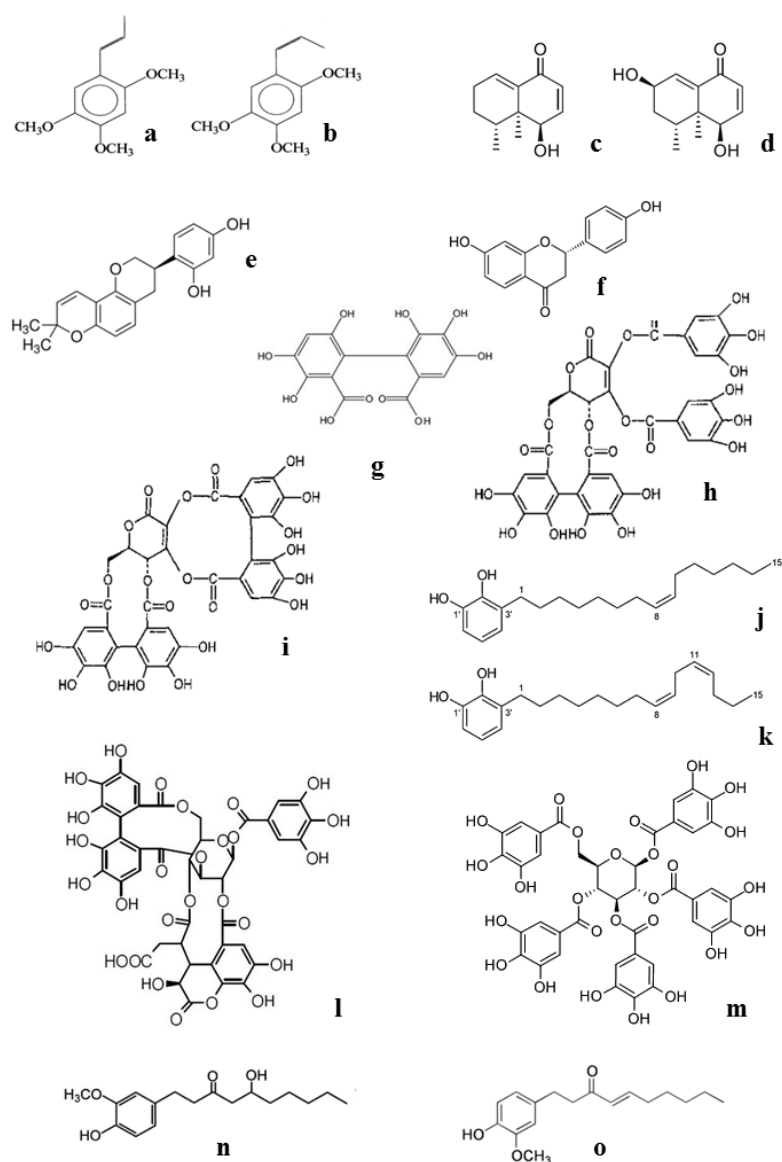
Mohammad Mahdi Ahmadian-Attari and Solat Eslami were participated in study concept and design, acquisition of data, and drafting of the manuscript; Leila Dargahi was participated in analysis and interpretation of data; Ahmad Ali Noorbala was participated in study concept and design and critical revision of the manuscript.

#### Conflict of interest

The authors declared no conflict of interest.

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**Fig. 2. Active anti-dementia compositions of herbs commonly used in Chinese, Indian, and Iranian traditional medicine. a:**  $\alpha$ -asarone; **b:**  $\beta$ -asarone; **c:** desoxo-narchinol A; **d:** narchinol B; **e:** glabridin; **f:** liquiritigenin; **g:** 3, 5, 6, 3', 5', 6'-hexahydroxybiphenyl-2, 2'-dicarboxylic acid; **h:** emblicanin a; **i:** emblicanin b; **j:** 1',2'-dihydroxy-3'-pentadec-8-enylbenzene; **k:** 1',2'-dihydroxy-3'-pentadeca-8,11-dienylbenzene; **l:** chebulagic acid; **m:** 1,2,3,4,6-penta-O-galloyl- $\beta$ -D-glucose; **n:** 6-gingerol; **o:** 6-shogaol.

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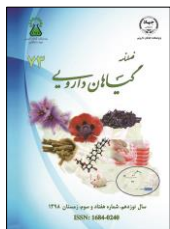
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مقاله مروری

### درمان‌های گیاهی مشترک برای زوال عقل سالمندی در تمدنهای باستانی: تمدن یونان و روم، چین، هند و ایران

محمد مهدی احمدیان عطاری<sup>۱،۲</sup>، صولت اسلامی<sup>۳</sup>، لیلا درگاهی<sup>۴</sup>، احمدعلی نوربالا<sup>۵\*</sup>

<sup>۱</sup>مرکز تحقیقات گیاه درمانی و طب مکمل مبتنی بر شواهد، دانشگاه علوم پزشکی البرز، کرج، ایران

<sup>۲</sup>گروه فارماکوتکونومی، دانشکده داروسازی، دانشگاه علوم پزشکی البرز، کرج، ایران

<sup>۳</sup>مرکز تحقیقات پروبیوتیک و مکمل‌های غذایی، دانشگاه علوم پزشکی البرز، کرج، ایران

<sup>۴</sup>مرکز تحقیقات نوروبیولوژی، دانشگاه علوم پزشکی شهید بهشتی، تهران، ایران

<sup>۵</sup>بخش روان‌تنی بیمارستان امام خمینی، دانشگاه علوم پزشکی تهران، تهران، ایران

#### اطلاعات مقاله

#### چکیده

گل‌واژگان:

زوال عقل

بیماری آلزایمر

طب سنتی

ترکیبات طبیعی

گیاه درمانی مبتنی بر شواهد

**مقدمه:** زوال عقل سالمندی شایع‌ترین نوع زوال عقل با هزینه‌های قابل ملاحظه اجتماعی و اقتصادی است. ماهیت این بیماری پیچیده است و درمان‌های رایج نتوانسته‌اند همه جنبه‌های این بیماری را پوشش دهند. اخیراً تمرکز بر ترکیبات طبیعی مخصوصاً موادی که سابقه مصرف سنتی دارند در دستور کار مطالعات علمی است. **هدف:** هدف این مطالعه بررسی درمانهای مشترک زوال عقل در طب باستانی یونان، طب سنتی چین، هند و ایران با تمرکز بر گیاهانی است که حداقل در دو تمدن به این عنوان ذکر شده باشد. **روش بررسی:** پایگاه اسکوپوس و منابع دست اول طب سنتی برای واژگان منتخب این تحقیق جستجو شدند. سپس گیاهان مشترکی که حداقل در دو طب سنتی برای زوال عقل کاربرد داشتند مورد بررسی مواد مؤثره و مکانیسم اثر دارویی قرار گرفتند. **نتایج:** گیاهان وح، سنبل هندی، شیرین بیان، آمله، بلادر، بلبله و زنجبیل در طب‌های سنتی پیشگفت برای زوال عقل تجویز می‌شده‌اند. مطالعات فارماکولوژیک نشان می‌دهد این گیاهان اثر ضد زوال عقل خود را از طریق مهار استیل کولین استراز، مهار NMDA، اثر آنتی‌اکسیدانی، ضد التهابی، ضد آپوپتوزی و جلوگیری از تشکیل پلاک بتا-آمیلوئیدی بروز می‌دهند. همچنین، شانزده ماده فعال دارویی ضد آلزایمری شامل آلفا و بتا-آسارون، دزوکسو-نارکینول آ، نارکینول بی، گلابریدین، لیکوئیریتینزین، امبلیکانین آ و بی، جبولاژیک اسید، زینچیپائین، ۶-جینجروول، ۶-شوگائول و چند ماده دیگر در این گیاهان شناسایی شده‌اند. **نتیجه‌گیری:** طب سنتی چین، هند و ایران می‌توانند نقش مکمل در پیشگیری و درمان زوال عقل سالمندی ایفا کنند. شواهد علمی از آثار سنتی ضد آلزایمر درمان‌های آنها پشتیبانی می‌کند.

مخفف‌ها: Acetylcholinesterase Inhibitor (AChEI); Alzheimer's disease (AD); Beta amyloid (A $\beta$ ); Butyrylcholinesterase inhibitor (BuChEI); Iranian traditional medicine (ITM); N-Methyl-D-aspartic acid (NMDA); Traditional Chinese medicine (TCM)

\* نویسنده مسؤول: [noorbala@tums.ac.ir](mailto:noorbala@tums.ac.ir)

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