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Short-Communication

Almond for mild to moderate Alzheimer's disease: A randomized clinical trial

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Abstract

Objective: Almonds are frequently advised as brain tonic and memory enhancers in Persian medicine. There is also scientific evidence to support the effects of almond on memory. This study was designed to assess the effects of almond (*Prunus dulcis*) on memory and cognitive functions in patients with Alzheimer's disease (AD).

Materials and Methods: In this randomized controlled trial, 60 AD patients with mild to moderate cognitive disorder were randomly allocated into an almond group (10 g/day powdered sweet almond plus 1 teaspoon of powdered rock candy along with their previous prescriptions), or the control group (continue previous prescriptions) for 3 months. The Mini–mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Clinical Dementia Rating (CDR), and Functional Assessment Staging (FAST) questionnaires were completed at the beginning and the end of the study. The sleep quality was also assessed by the Pittsburg Sleep Quality Index (PSQI).

Results: Thirty participants in each group completed the study, and were analyzed. Age was 71.86±8.04 years in the almond group and 71.3±7.18 years in the control group (p=0.775). Duration of memory deficit was 2.8±0.92 and 3±1.2 months in the almond and control group, respectively (p=0.473). The orientation scale of the MMSE (p=0.024), MOCA (p=0.001), memory scale of MOCA (p=0.005), FAST (p=0.032), and PSQI (p<0.001) in the almond group were significantly improved compared to those in the control group.

Conclusion: Almond is a probable safe intervention for memory and sleep enhancement in AD patients. Conducting studies with larger samples, longer follow-up periods, and different control groups are suggested.

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Introduction

Aging and its physical and mental disorders constitute a public health problem worldwide. Dementia is a common mental disorder in individuals older than 60 years (El-Hayek et al. 2019) with an increasing

prevalence worldwide (Prince et al. 2013). Alzheimer's disease (AD) which accounts for approximately 60 to 80% of cases of dementia, is the third cause of death in the United States (Organization 2017; Scheltens et al. 2021). AD is a progressive neurodegenerative disorder with cognitive and memory impairments, psychological and behavioral findings, problems in the patient's function, language dysfunction, and difficulty in performing learned motor tasks (Markowitsch and Staniloiu 2012).

In a study done in Iran, more than 36% of elderly inpatients had some degree of cognitive impairment (Kamalzadeh et al. 2019). The prevalence of dementia was reported as 7.9% among people aged 60 years or older (Sharifi et al. 2016), and the prevalence of AD was estimated as 2.3% of the population of 67-78 years old in Iran (Navipour et al. 2019).

Average costs of dementia have been estimated at up to £46,050 per person per year in England (Wittenberg et al. 2019), and up to 2480 USD per person per year in Iran (Aajami, Kebriaeezadeh and Nikfar 2019), which mentions a serious burden to public health and social welfare organizations.

Data on pathological and physiological mechanisms of AD are controversial. Amyloid plaques, neuronal loss, neurofibrillary tangles, and synapses, are the core pathological hallmarks recognized in AD (DeTure and Dickson 2019; Lashley et al. 2018; Prasansuklab and Tencomnao 2013; Selkoe and Hardy 2016).

FDA (Food and Drug Administration)-approved medications used for the management of AD are cholinesterase inhibitors (ChEIs; donepezil, galantamine, and rivastigmine) and memantine (Long and Holtzman 2019), however, the management of AD remains a challenge, and exploring new medications for preventing or slowing the progression of this disease is needed.

In the last few years, there has been increased use of herbal medications for different disorders in all countries (Menghani et al. 2021; Santos-Neto et al. 2006). Herbs and herbal remedies have a long history of traditional use (Abascal and Yarnell 2004; Rao et al. 2012). *Ginkgo biloba, Zingiber officinalis, Rosmarinus officinalis, Salvia officinalis, Crocus sativus, Emblica officinalis, Coriandrom sativum,* and *Curcuma longa* are some of the plants that have been used in *in-vitro* or *in-vivo* studies and their effects on dementia have been presented. Herbal constituents such as monoterpene aldehydes, polyphenols, flavonoids, and monoterpene glycosides which have anti-oxidative, anti-inflammatory, and neuroprotective activity, or act as nicotinic and muscarinic receptor agonists in the human cerebral cortex, could modulate the cholinergic systems and should improve the memory and cognitive function (Abascal and Yarnell 2004; Khazdair et al. 2019; Santos-Neto et al. 2006).

Almond or sweet almond with the scientific name of *Prunus dulcis* (Rosaceae family), "*Lawz*" or "*Badam*" in Persian medicine (PM), is one of the most important brain tonic and memory enhancer nuts and is frequently advised for the treatment of some brain disorders (Karimi et al. 2020).

Modern pharmacological studies present several biological activities of *P. dulcis* including the pre-biotic, antimicrobial, antioxidant, anti-inflammatory, anticancer, laxative, hepatoprotective, neuroprotective, cardioprotective, nootropic, anxiolytic, sedative, and hypnotic effects (Karimi et al. 2020).

Some pathways in the pathogenesis of AD such as amyloidogenesis, and cholinergic pathways could be affected by almond phytochemicals. In addition, the antioxidant, anti-inflammatory, and cholesterol-lowering effects of almonds could be efficient in preventing or managing the symptoms of AD (Gorji, Moeini and Memariani 2018). The memory-enhancing effect and cholinesterase inhibitory activity of almonds have been presented in animal studies (Batool et al. 2016; Batool et al. 2018; Haider, Batool and Haleem 2012; Kulkarni, Kasture and Mengi 2010). In a clinical trial, receiving 3 oz/day almonds for

6 months resulted in a significant improvement in visuospatial working memory, visual memory, learning, spatial planning, and working memory in healthy adults (Mustra Rakic et al. 2022).

Since no research has been done on the effect of almonds in patients with AD, the present study was designed and conducted for investigating the effect of almonds on the cognitive and functional status of patients with AD.

Materials and Methods

Trial design

This study is a randomized controlled trial.

Participants

This trial was conducted in the Alzheimer's Association of Iran (Tehran, Iran) from December 2022 to May 2023. Participants were informed about the objectives and method of the present study before signing the consent form. The potential efficacy and side effects of the interventions, and the advantages and disadvantages of participating in the study were also explained. In addition, participants were free to leave the study at any time they wanted. Confidentiality was considered during the study, analysis of data and presentation of the results.

Inclusion criteria were AD patients with the Mini-Mental State Examination (MMSE) scores between 18 and 23 (mild cognitive disorder) and confirmation of a geriatric physician (Dubois et al. 2021), written informed consent, age 60-95 years, rule out the other causes of dementia, and having a good nurse or family caregiver.

Exclusion criteria were any changes in medications and lifestyle at least 3 months before the study, vision, and hearing problems, severe disabilities, cardiovascular diseases, cerebrovascular diseases, drug abuse or alcohol dependence, diabetes mellitus, or epilepsy.

Having a desire to leave the project at any stage, cognitive disorders interfering with treatment such as delirium, changes in medications and lifestyle during the study period, and medication adherence of less than 80% were considered attrition criteria.

Randomization

Randomization was done using Random Allocation software, considering a block randomization method with a random block size. Sealed envelopes were used to ensure random allocation concealment. Blinding of patients was not possible due to the type of intervention.

Calculation of sample size

The sample size was calculated as 30 patients in each group using G* power software (version 3.1, freely downloaded from the internet), considering type one error = 0.05, power = 0.8, and the effect size 0.65 for the scores of all questionnaires used in the study.

Interventions

Intervention in one group was 10 g powdered sweet almond plus 1 teaspoon of powdered rock candy ("*nabat*") once daily for 3 months. Dose of almond in this study was based on the experimental information of traditional healers. Almonds were bought from the central Zagros area (Iran), powdered, and packed before use. One package was prescribed to each patient at each visit to be consumed during 1 month.

The other group was followed without any intervention for 3 months. Patients were allowed to continue their previous medication regimens without any changes.

Participants were visited once a month for delivering the medications and measuring their medication adherence.

Outcome measures

Outcomes were cognitive impairment which was measured by the Persian versions of MMSE (Ansari et al. 2010), Montreal Cognitive Assessment (MoCA) (Rashedi, Foroughan and Chehrehnegar 2021), Clinical Dementia Rating (CDR) questionnaires (Sadeghi et al. 2012). The

social work performance was measured by the Persian version of Functional Assessment Staging (FAST) questionnaire (Noroozian et al. 2022). All questionnaires were completed by patients at the beginning and the end of the study. A doctor was responsible to the patients' disambiguations.

MMSE is a standard tool that evaluates memory, orientation, language, attention and calculation, and the ability to follow simple commands. The maximum score is 30, 24-30 is a normal range of cognition, 18-23 is considered mild cognitive impairment, and 0 to 17 indicates severe cognitive impairment (Ansari et al. 2010).

FAST is a questionnaire that examines the social work performance and normal life of the elderly patient from the point of view of the patient and her family members and compares it to a few years ago. Its reliability and validity for evaluating the functional decline in AD have been approved (Noroozian et al. 2022).

CDR scale measures short-term and long-term memory. This tool has 75 items in 6 areas, "memory", "time and place orientation", "judgment and problem solving", "social affairs", "home and entertainment" and "personal affairs"; Each area has a separate score in the range of 0 to 3 (0.5, 1, 2, and 3); the higher the score, the worse the cognitive condition of the person (Sadeghi et al. 2012).

MoCA is another tool for screening of cognitive disorders including AD. The test consists of 30 points in seven stages and assesses several cognitive domains, including short-term memory, peripheral-temporal awareness, multiple aspects of executive functions, attention, concentration, working memory, language, abstract Reasoning, and time and place orientation (Rashedi, Foroughan and Chehrehnegar 2021).

Adverse reactions and sleep quality were assessed as the secondary outcomes of the study. Pittsburg Sleep Quality Index (PSQI) is a frequently used tool for assessing the quality of sleep. It has 7 questions and a four-point Likert scale (from 0 to 3) for the answers, and the higher the score, the worse the sleep quality (Mohammad Gholi Mezerji et al. 2017). Adverse reactions were evaluated by a checklist containing some frequent sign and symptoms and an open-ended question.

A diary note was completed by patients' caregivers to ensure the correct use of the prescribed intervention. Adherence to research protocol was assessed by checking the diary notes, and the amounts of powdered almonds brought back by patients at follow-up visits.

Statistical analysis

Data were analyzed using SPSS software (version 27). Quantitative variables are presented as mean and standard deviation. Frequency of qualitative data were also presented. Quantitative variables were compared between the two groups with non-parametric tests (Mann-Whitney U) and qualitative variables were compared between the two groups with Chi-square or Fisher's exact test. Wilcoxon signed-rank test was used to compare quantitative variables within each group. A 0.05 was considered a significant level for the main variable.

Results

Thirty patients in each group completed the study and entered the analysis. Figure 1 shows the CONSORT flow diagram in this study. Patients were 60 to 89 years old and the mean and standard deviation (SD) of age was 71.58 (7.56) years. 22 patients in the almond group and 12 patients in the control group were female (p=0.018). Two groups were statistically identical for age and duration of AD, but not for sex, as presented in Table 1.

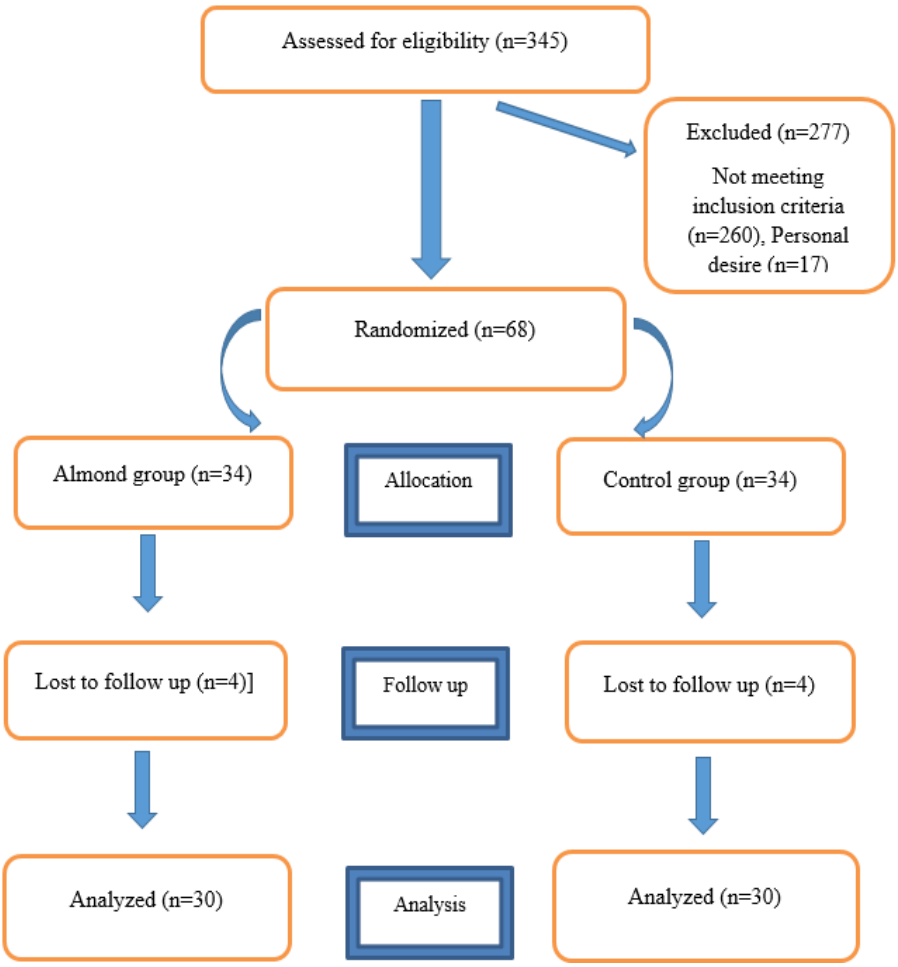

Figure 1. The CONSORT flow diagram of the stud

Table 1. Age, sex, and severity of AD of the patients of the two groups at baseline

	Almond group	Control group	p-value
Age Mean(SD), (year)	71.86(8.04)	71.3(7.18)	0.775
Sex n (%)	Female:22(73.3) Male: 8(26.7)	Female: 12(40) Male:18(60)	0.018
Duration of disease Mean(SD),(month)	2.8(0.92)	3(1.2)	0.473

SD: standard deviation

Table 2 shows the scores of MMSE, MoCA, and CDR before and after 3 months of follow-up in both groups.

According to Table 2, the MMSE score was significantly improved in the almond group (p=0.001), but no significant change was observed in the control group (p=0.739). The MMSE orientation score was significantly improved in the almond group (p=0.011), and this improvement was significantly higher than that in the control group (p=0.024). The MMSE cognition score was not significantly changed in any groups, and the changes were similar between groups (p=0.832). The MOCA score showed a significant improvement in the almond group (p<0.001) while no significant change was observed in the control group (p=1.000).

The MOCA visual scale had no significant change in any groups (p=1.000 for the almond group and p=0.317 for the control group). The MOCA memory score showed a significant improvement in the almond group (p<0.001), and no change in the control group (p=0.157). Changes in the MOCA attention score were not significantly different between (p=0.776) and within groups (p=0.414 for the almond group and p=0.655 for the control group). Changes of the CDR scores were similar in two groups (p=1.000).

Table 3 presents the number of patients in each class of the FAST scale during the study. According to this Table, number of patients who came down to a lower class of this Table was significantly higher in the almond group than the control group (p=0.022).

The change of PSQI score was 10.89% (10.45) in the almond group, and 1.66% (5.18) in the control group (p<0.001), which shows more improvement in sleep quality in the almond group than in the control group.

No adverse effect was observed in the almond group during the study.

Table 2. MMSE, MOCA, and CDR scores in each group during the study

	groups	**Baseline Mean(SD)**	**After 3 months Mean(SD)**	**✱p value**	**Percent of changes during the study Mean(SD)**	**✱✱p value**	**Cohen's effect size**
MMSE	Almond group	22.93(0.25)	23.33(0.6)	0.001	-1.74(2.45)	0.058	
	Control group	20.53(1.65)	20.56(1.69)	0.739	-0.18(2.79)		
MMSE,	Almond group	8.96(0.76)	9.23(0.77)	0.011	3.16(6.1)	0.024	0.55
orientation scale	Control group	7(1.48)	6.93(1.5)	0.480	0.68(7.74)		
MMSE,	Almond group	15.23(1.35)	15.36(1.24)	0.102	0.98(3.03)	0.832	
cognition scale	Control group	13.73(1.22)	13.83(1.14)	0.527	1(6.8)		
MOCA	Almond group	23.86(1.7)	24.46(1.94)	<0.001	-2.47(2.34)	0.001	1.03
	Control group	22.3(1.74)	22.3(1.8)	1	-0.004(2.43)		
MOCA,	Almond group	2.56(1.35)	2.56(1.35)	1	0	0.334	
visual scale	Control group	2. 6(1.06)	2.56(1.04)	0.317	0.83(4.56)		
MOCA,	Almond group	3.23(0.72)	3.73(0.78)	<0.001	-16.94(17.97)	0.005	0.52
memory scale	Control group	3.03(0.71)	3.16(0.69)	0.157	-6.38(22.06)		
MOCA,	Almond group	5.26(1.04)	5.2(1.15)	0.414	1.33(8.99)	0.776	
attention scale	Control group	4.86(1.25)	4.83(1.31)	0.655	0.66(10.84)		
CDR	Almond group	15.6(0.72)	15.6(0.72)	1	-0.13(1.69)	1	
	Control group	15.3(0.53)	15.3(0.53)	1	0		

SD: standard deviation, ✱: Wilcoxon signed rank test, ✱✱: Mann-Whitney U test

Table 3. FAST score in each group during the study

	FAST score	**Almond group n (%)**	**Control group n (%)**	**p-value**
Baseline	4	29(96.7)	25(83.3)	0.195
	5	1(3.3)	5(16.7)	
After 3 months	3	8(26.7)	1(3.3)	0.022
	4	21(70)	25(83.3)	
	5	1(3.3)	4(13.3)	

FAST score 3: Mild Cognitive Impairment, 4: mild AD, 5: moderate AD

Discussion

The present study showed a significant improvement in the cognition, memory, and orientation status, and functional performance of patients in the almond group was greater than that of the control group.

The rising incidence of AD makes it a challenging neurological disorder and a global health issue. In recent years, research on natural products has been done to find potential treatments for AD.

Tree nuts and their properties to protect the brain have been considered in many research studies and in traditional medicinal systems like Persian Medicine (PM) (Aghili-Khorasani MH 2001). Almonds and other nuts have some bioactive components that are potentially efficient in the protection or treatment of AD. PUFA (poly unsaturated fatty acids) and MUFA (mono unsaturated fatty acids) are the major ingredients of almonds. Almond also contains amounts of protein, vitamins, and minerals, tocopherol, folate, and polyphenolic compounds including morin, quercetin, quercitrin, and kaempferol which have antioxidant and potentially neuroprotective properties (Torabian et al. 2009; Wijeratne, Abou-Zaid and Shahidi 2006). Polyphenols have been known to be protective against or delay the onset of neurodegenerative diseases, and age-associated cognitive dysfunction. *P. dulcis* is a source of almost 130 different polyphenols (Alasalvar and Bolling 2015).

The cholinergic neuronal systems are mainly involved system in cognitive disorders during aging, neurodegenerative diseases, and AD (Ellis 2005; Jelic and Winblad 2021; Kabir et al. 2019; Sharma 2019). It has been shown that four weeks of administration of almond suspension (400 mg/kg/day) in healthy rats, increased brain acetylcholine levels and improved memory function (Batool et al. 2016).

Another study showed that pre-treatment with 400 mg/kg/day almond suspension in a group of rats for 28 days before inducing amnesia, significantly ameliorated scopolamine-induced oxidative stress and memory dysfunction. Almonds may reduce the risk of memory loss induced by oxidative stress and delay or prevent age-related memory deficit (Batool et al. 2018).

A study also showed that the administration of 400 mg/kg/day of almond supplement for 28 days significantly decreased the severity of cadmium-induced memory impairment in rats, and increased acetylcholinesterase activity in the frontal cortex and hippocampus. This result was associated with decreasing malondialdehyde levels in the almond group which had been increased following the administration of cadmium (Batool et al. 2017).

In another animal study, rats were fed with almond paste orally for 28 days. Memory function, brain tryptophan (TRP), 5-hydroxy tryptamine, and 5-hydroxy indole acetic acid were estimated at the end of the treatment. Almond-treated rats exhibited a significant improvement in learning and memory, a significant decrease in food intake and plasma cholesterol levels, and an increase in TRP levels and serotonergic turnover in the brain compared to control groups (Haider, Batool and Haleem 2012).

Kulkarni et al. also suggested that almonds may be a useful memory-restorative agent because they observed a reduction in the choline esterase activity in the brains of rats with amnesia, and an increment in their memory after being fed a diet containing 300 and 600 mg/kg almond for 7 and 14 days (Kulkarni, Kasture and Mengi 2010).

The main histological features of AD include extracellular deposits of amyloid beta (AB), in blood vessels, and intraneuronal neurofibrillary tangles (Agnati et al. 2007). Cell and animal studies of AD showed that abnormal levels of cholesterol increase AB, and inhibiting the synthesis of cholesterol could decrease AB (Refolo et al. 2000). Kulkarni et al. showed a significant reduction in cholesterol and

triglyceride levels in animals treated with almonds as compared to the control groups (Kulkarni, Kasture and Mengi 2010).

To evaluate the effects of almonds on blood lipid profile in a clinical trial, 10 ml of almond oil two times daily for 30 days was administered to patients with hyperlipidemia, and compared with no intervention. The total cholesterol and low density lipoprotein (LDL) levels decreased significantly in the intervention group, while triglyceride and high density lipoprotein (HDL) did not change (Zibaeenezhad et al. 2019)).

A review of the effect of almonds on weight, metabolic biomarkers of health, and the colonic microbiota, was conducted by Dreher et al., and showed that almonds decreased mean body mass and fat mass, compared to control diets, and some biological mechanisms for the effect of almond on weight were explained (Dreher, 2021). Some RCTs show that promoting microflora richness and diversity, and increasing the ratio of symbiotic pathogenic microflora, and concentrations of health-promoting colonic bacteria that occur from almonds can support colonic microbiota health (Creedon et al. 2020; Dreher 2021). Some studies in rodents suggest that changes in the gut microbiome may be associated with amyloid deposition in the brain. Vogt et al. revealed a compositional difference between the gut and brain microbiome in AD patients and age- and sex-matched individuals. These findings suggested that AD might be a disease associated with gut microbial alterations, and therapeutic interventions should consider the microbiome an important target (Vogt et al. 2017).

Mustra Rakic et al. conducted a six-month randomized controlled trial to compare the effects of almonds (1.5 and 3 oz/day) on cognition in healthy 50–75-year-old adults. Serum tocopherols, oxidative status and inflammation, and cognition were assessed at baseline, and three, and six months after intervention. Significant improvements in visuospatial working memory, visual memory and learning, spatial planning, and working memory were observed in subjects receiving 3 oz/d almond after 6 months, while no improvement was observed in the control group (Mustra Rakic et al. 2022).

The present study showed a significantly improved sleep quality in the almond group compared to the control group. The relationship between sleep and AD is not approved, however, sleep disturbances are common health problems in dementia and neurodegenerative disorders (Cipriani et al. 2015; Lucey et al. 2021). It is also said that sleep disturbances might increase the risk of dementia, and AD (Kuang et al. 2021; Shi et al. 2018). Neurodegenerative disease and sleep may influence each other in many ways. Levels of beta amyloids (Aβ) in the brain are directly influenced by the sleep-wake cycle. On the other hand, experimental models exhibited increases in the concentration of soluble Aβ during sleep deprivation. Aβ accumulation in the brain increases wakefulness and alters sleep patterns (Ju, Lucey and Holtzman 2014). *Prunus dulcis* presented anxiolytic (Sahib 2014), sedative, and hypnotic effects in animal studies (Abdollahnejad et al. 2016). In a study, consumption of 400 mg/kg of almonds 30 minbefore sleeping for 2 weeks, showed improvement in sleep time, percentage of sleep efficiency, and sleep onset latency in patients (n=13) with sleep disturbances (Noor and Othman 2020). Ghafarzadeh et al. also showed a significant impact of sweet almonds on the sleep quality of a group of university students in a quasi-experimental study. This study presented that eating 10 sweet almonds per day for two weeks significantly reduced the severity of insomnia (Ghafarzadeh et al. 2019).

In PM, almond is considered a “brain food” that increases mental alertness, concentration, and memory and improves recall skills, and sleep quality (Aghili-Khorasani MH 2001). Sugar or “*nabat*” consumption with almonds is frequently

advised in PM texts for memory improvement and neuroprotection (Aghili-Khorasani MH 2001).

One of the limitations of the present study was the small sample size and a short duration of the study which was due to the limitation of time and budget. Larger studies with different dosage of almond, different control groups and longer duration are suggested for better assessment of the effects of almonds in AD patients.

Almond is a safe intervention for the improvement of the cognition, orientation and memory status, functional performance, and sleep quality in patients with AD. Larger studies with longer follow-up periods are suggested.

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Conflicts of interest

There is no conflict of interest to declare.

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Ethical Considerations

The approval ID of IR.IUMS.REC.1399.1001 was obtained from the research ethics committee of Iran University of Medical Sciences and the protocol was registered at www.irct.irwww.irct.ir (IRCT20231031059912N1).

Authors' Contributions

S.M proposed the title, S.M., M.M., F.H.D, and Sh.R. designed the protocol. M.M gathered the data. F.H.D. analyzed the data and interpreted the results. M.M. drafted the article and other authors completed that.

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