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Comparing the efficacy and safety of *Crocus sativus* L. with memantine in patients with moderate to severe Alzheimer's disease: a double-blind randomized clinical trial

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Objectives Limited pharmacological options are available for the management of Alzheimer's disease (AD) in severe stages. Cognitive-enhancing properties of saffron, the dried stigma of *Crocus sativus* L., have been evidenced in different studies. We aimed to compare the efficacy and safety of saffron extract versus memantine in reducing cognitive deterioration of patients with moderate to severe AD.
Methods In this randomized double-blind parallel-group study, 68 patients with moderate to severe AD (Mini-Mental State Examination score of 8–14) received memantine (20 mg/day) or saffron extract (30 mg/day) capsules for 12 months. Participants were evaluated every month by Severe Cognitive Impairment Rating Scale (SCIRS) and Functional Assessment Staging (FAST) in addition to recording the probable adverse events.
Results Both treatment groups showed similar outcomes as demonstrated by insignificant effect for time × treatment interaction on SCIRS scores [$F(2.95, 194.78) = 2.25, p = 0.08$]. There was no significant difference between the two groups in the scores changes from baseline to the endpoint on SCIRS ($p = 0.38$) and FAST ($p = 0.87$). The frequency of adverse events was not significantly different between the two groups as well.
Conclusions In addition to its favorable safety profile, 1-year administration of saffron extract capsules showed to be comparable with memantine in reducing cognitive decline in patients with moderate to severe AD. Confirmatory studies with larger sample sizes and longer follow-up periods are warranted. Copyright © 2014 John Wiley & Sons, Ltd.

KEY WORDS—saffron; memantine; Alzheimer's disease; *Crocus sativus* L.; glutamate

INTRODUCTION

Alzheimer's disease (AD), the leading cause of dementia worldwide, is an irreversible progressive neurodegenerative disorder characterized by cognitive impairment and functional disability (Cummings and Cole, 2002). The devastating nature of AD leads to serious social and economic impacts on the healthcare systems, which implies the necessity of its proper management (Zhao *et al*., 2008). It has been demonstrated that patients' quality of life and their overall prognosis have a significant negative correlation with the severity of AD. Patients with severe AD need full-time care and assistance with some basic activities of daily living such as feeding and dressing in addition to severe deterioration in various domains of their cognitive functioning (Auer *et al*., 1994; Herrmann and Gauthier, 2008). Moreover, behavioral aberrancy and neuropsychiatric symptoms such as depression, apathy, psychosis, agitation, and aggression are observed more frequently in moderate to severe AD (Johnson *et al*., 2011). Despite such an enormous burden, most practical guidelines focus on mild to moderate stages of the illness, and there is still a serious lack of evidence regarding the management of severe AD. Among currently Food and Drug Administration-approved drugs, very few medications have shown to be effective in attenuating some of the AD-related symptoms in severe stages. Memantine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, and donepezil, an acetylcholinesterase inhibitor (ACEI), are the most widely accepted agents in this regard (Herrmann and Gauthier, 2008; Hsiung and Feldman, 2008). Unfavorable side effects of these agents along with lack of optimal efficacy have led to many researches trying to find novel pharmacologic strategies for AD based on its underlying pathophysiological defects (Forchetti, 2005).

Considering their acceptable efficacy and a more favorable safety profile, herbal remedies have attracted

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more attention as novel promising entities for improving or at least decreasing cognitive deterioration in patients with AD (Akhondzadeh and Abbasi, 2006). Effectiveness of herbal compounds in counteracting different central nervous system-affecting disorders and cognitive deficits has been determined in numerous experimental and clinical researches (Kumar, 2006; Kennedy and Wightman, 2011). Saffron is the dried stigma of a plant named *Crocus sativus* L. and has been known as the world's most expensive spice and a widely used medicinal plant. From a chemical standpoint, the main constituents of saffron are carotenoids (crocin), esters (crocetin), and aldehydes (picrocrocin and safranal) (Melnyk *et al*., 2010). In the recent decades, a growing body of evidence has revealed encouraging beneficial effects for saffron in treating different neuropsychiatric disorders such as depression, seizure, anxiety, and memory disorders (Srivastava *et al*., 2010; Modabbernia and Akhondzadeh, 2013). Similarly, promising advantages of saffron in improving different cognitive functions have been demonstrated in multiple preclinical studies. Saffron administration in animals can reverse memory deficits in different behavioral tasks, exerts protective effects against neuronal injury, and positively affects learning behavior, recognition, spatial memory, and long-term potentiation (Zhang *et al*., 1994; Abe and Saito, 2000; Pitsikas and Sakellaridis, 2006; Ochiai *et al*., 2007; Pitsikas *et al*., 2007; Ghadrdoost *et al*., 2011).

Although not completely investigated yet, different mechanisms of action may underlie neuroprotective potentials of saffron in antagonized decay of cognitive faculties of the brain. Aggregation and deposition of beta-amyloid (Aβ) peptides is the main molecular process underlying AD, and saffron constituents can interact with these peptides, inhibiting Aβ fibrillization and amyloid formation (Papandreou *et al*., 2006; Ahn *et al*., 2011; Prasansuklab and Tencomnao, 2013). It has been evidenced that oxidative stress and its subsequent neuronal damage play a key role in AD pathogenesis (Moreira *et al*., 2005). Antioxidant capability of saffron and its particular relation to memory-enhancing effects of this compound have been well studied and recognized (Papandreou *et al*., 2011; Serrano-Diaz *et al*., 2012). Furthermore, glutamatergic system dysfunction has been recently suggested as another pathophysiological process in developing AD. In addition to its bidirectional relation with amyloid production, glutamate is a central component in developing and performing higher cortical functions. Overactivation of NMDA receptors ultimately leads to neuronal injury and death, a known process in the AD development and progress (Riederer and Hoyer, 2006; Revett *et al*., 2013). Interestingly, saffron constituents have been shown to decrease extracellular glutamate levels and exert antagonist effects on NMDA receptors (Hosseinzadeh *et al*., 2008; Berger *et al*., 2011; Ohno *et al*., 2012), a function that can be compared with memantine's mechanism of action. Moreover, ACEIs have become the cornerstone of AD treatment on the basis of various evidences indicating cholinergic hypofunction in different brain regions of the affected individuals (Chopra *et al*., 2011). It has been shown that saffron constituents can moderately inhibit acetylcholinesterase activity and thereby increase the acetylcholine levels (Geromichalos *et al*., 2012), another mechanism that further suggests beneficial effects for saffron in AD.

In terms of clinical studies, we previously investigated the efficacy and safety of saffron for mild to moderate AD in two separate clinical trials. In the first 16-week clinical trial, saffron-treated patients experienced significantly greater improvement in cognitive scales than the placebo group, and no significant difference was detected between two groups in the frequency side effects (Akhondzadeh *et al*., 2010a). In another clinical trial, saffron and donepezil capsules were separately administered to 54 patients with mild to moderate AD for 22 weeks, and the patients' cognitive outcomes were compared. Saffron showed to be comparable with donepezil in this study with significantly lower rates of side effects (Akhondzadeh *et al*., 2010b). On the basis of the existing evidences, it can be hypothesized that treatment with saffron would be of benefit for patients suffering from more severe stages of AD. Memantine is a Food and Drug Administration-approved medication for moderate to severe AD, and patients with milder forms of the disease may not benefit from that (Schneider *et al*., 2011). We designed the present 1-year clinical trial in order to compare the efficacy and safety of saffron with memantine in improving or reducing the cognitive deterioration in patients suffering from moderate to severe AD.

METHODS

Trial design

This was a parallel-group, double-blind randomized clinical trial in which patients were treated and followed up for 12 months. The trial protocol was registered at the Iranian Clinical Trials Registry (IRCT201203051556N39; www.irct.ir), approved by the institutional review board of the Tehran University of Medical Sciences (approval code: 16712) and performed in accordance with the Declaration of

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Helsinki and its subsequent revisions. After a complete description of the study details, written informed consent was obtained from eligible participants and/or their legal representative. Patients were informed about their right to withdraw from the study at any time without any negative effect on their relationship with the healthcare providers.

Participants

Inclusion criteria. Male and female outpatients older than 60 years were eligible to participate if they met the criteria for dementia according to the Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision as well as the criteria for a diagnosis of AD based on the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (McKhann *et al*., 1984). Other inclusion criteria were a Mini-Mental State Examination (MMSE) score of 8–14 at baseline, a history of cognitive decline that had been gradual in onset and progressive for at least 6 months, and a brain computed tomography or magnetic resonance imaging (MRI) scan within 1 year before enrolment consistent with the diagnosis and not indicative of an active cerebrovascular disorder or multi-infarct dementia. Patients were required to have sufficient hearing and vision to comply with the assessments, be accompanied with a knowledgeable person in all trial visits, and be supervised by a reliable caregiver for administration of the trial medications. Patients were not included if they had been previously treated with saffron or memantine. Previous ACEIs must have been discontinued at least 2 months before randomization and that such discontinuation was not solely for the purpose of study enrolment but for other reasons such as no response or incompliance with the medications.

Exclusion criteria. Patients were excluded from this trial if they had a current Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision diagnosis of major depressive disorder, any psychiatric or neurodegenerative disorder other than AD, dementia complicated by delirium, significant cardiovascular disease likely to interfere with their participation and completion of the study, or any other uncontrolled medical problem such as hypertension, hypothyroidism, active peptic ulcer, chronic obstructive pulmonary disease, and renal failure. History of alcohol or substance abuse within the past 2 years, inability to communicate, and reported hypersensitivity to memantine or herbal compounds were considered as exclusion criteria as well.

Study settings

This clinical trial was conducted from March 2012 to August 2013 at the Memory Disorders Clinic of a referral academic hospital affiliated with the Mazandaran University of Medical Sciences. In 12 consecutive visits, patients were evaluated every month for 1 year after being screened and enrolled at the baseline session. There were no ethnical or regional restrictions for participation as patients are referred from different regions of the country to this large referral center.

Intervention

Eligible participants were equally randomized into two groups to receive either memantine (Ebixa®, Ebixa, Valby, Denmark, 10 mg) or saffron (Saffrotin®, Impiran, Tehran, Iran, 15 mg) for 12 months. The Saffrotin capsules used in this study were donated by the Green Plants of Life Co. and contained 15 mg dried extract of *C. sativus* L. Patients were planned to receive one capsule per day for the first month followed by two capsules per day for the rest of the study unless not tolerated. Therefore, the planned dose of memantine and saffron was 20 and 30 mg/day, respectively. Compliance with the study medications was assessed through checking with the patients and their caregivers in addition to a pill count at each visit. Patients were not allowed to receive any cognitive or behavioral therapy during the course of the trial. Psychotropic medications, sedative-hypnotics, and sedative cold remedies were withheld at least 48 h before performing the study evaluations.

The saffron capsules used in this study were prepared as follows: 120 g of dried and milled *C. sativus* L. stigma was extracted with 1800 mL ethanol (80%) by percolation procedure in three steps, and then the ethanol extract was dried by evaporation at a temperature of 35–40 °C. Each capsule contained dried extract of saffron (15 mg), lactose (filler), magnesium stearate (lubricant), and sodium starch glycolate (disintegrant). The most important compounds in saffron are crocin, picrocrocin, and safranal. Drug samples are evaluated by safranal and crocin values by means of a spectrophotometric method. Safranal and crocin values are expressed as direct reading of the absorbance at about 330 and 440 nm, respectively. The prepared extract was standardized by these two components: each capsule contained 1.65–1.75 mg of crocin.

Outcomes

The efficacy assessment measure used in this study was Severe Cognitive Impairment Rating Scale (SCIRS) by which patients were rated at baseline/screening session and each post-baseline visit. SCIRS is a valid and

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reliable test for assessing cognitive functions in severely demented individuals. It consists of 11 items covering memory, language, visuospatial function, frontal function, and orientation, and each patient is given a score of 0–30 based on that (Choe *et al*., 2008). In order to evaluate patients' overall functional disability and its changes, another measure called Functional Assessment Staging (FAST) was also completed during this study. FAST is a reliable scale validated for evaluating general functional capabilities, and patients are assigned to a stage of 1 (normal adult) to 7 (severe AD) by that (Sclan and Reisberg, 1992). Stages 6 and 7 are subdivided into further subcategories (a, b, etc.) on the basis of the severity of the patient's symptoms. In order to provide a statistically reliable analysis, stages 1, 2, 3, …, 7f on FAST were assigned to numerical values of −4, −3, −2, …, 11 because all of the study participants were suffering from moderate to severe AD (Grossberg *et al*., 2013). MMSE (Folstein *et al*., 1983) was also used for screening the severity of AD and was applied again at the study endpoint in order to provide a comparison with the baseline scores. The primary outcome of this study was the difference between saffron and memantine groups in change of SCIRS scores from baseline to the study endpoint. The number of patients who remained stable (≤10% change in SCIRS scores from baseline to the endpoint) throughout this study was also compared between the two groups. The difference between two study arms on the frequency of adverse events (AEs) as well as FAST and MMSE scores changes was considered as the study secondary outcomes.

Safety

Participants and their caregivers were strongly encouraged to immediately inform the research team about any unexpected symptom or complaint after entering the trial. A thorough physical examination was performed, and vital signs were recorded at the screening session and each post-baseline visit. Laboratory tests and electrocardiography were performed at baseline, month 6, and final visit. In addition to each post-baseline visit, AEs were recorded 2 weeks after the start of medications by a phone call. Possible AEs were assessed through open-ended questioning followed by a complete AEs checklist, a 25-item questionnaire covering a broad range of somatic complaints and warning symptoms. Cognitive assessments and AEs checklist were completed by independent raters. In case of encountering any AE, an expert neurologist was responsible for making decisions regarding whether to continue treatment, decrease dosage, or discontinue the medications.

Randomization

Patients were randomly and equally assigned to two groups (saffron or memantine) in a 1:1 ratio by means of the random allocation method. An independent person who was not involved elsewhere in the research project generated the randomization codes by Excel. The assignments were kept in sequentially numbered, sealed, opaque envelopes and were opened only after participant details were written on the envelope. Aluminum foil inside the envelopes rendered them impermeable to intense light. Separate persons were responsible for rating and random allocation of the patients.

Blinding

Study medications were packed in identical containers labeled by participants code numbers and were dispensed by an investigational drug pharmacist. Memantine tablets were put in capsules similar to saffron ones and were made identical in their coat, shape, size, odor, texture, and color. A synthetic essence with the saffron odor was also dispersed to the capsules containing memantine in order to make them similar in smelling. This essence was an aroma with no therapeutic effects. The patients and their caregivers, the clinician who referred them, the research team investigators who rated the participants and prescribed the medications, and the statistician were all blind to the treatment group assignments and medications.

Sample size and statistical methods

On the basis of previous trials, we assumed a final difference of 3 between the two groups on mean SCIRS scores with a standard deviation of 3, a power of 90%, a two-sided significance level of 0.05, and an attrition rate of 25%. Therefore, a sample size of 34 was calculated for each group. IBM SPSS Statistic 20 (IBM Corporation, Armonk, NY, USA) was used for data analysis. All analyses were based on the intention-to-treat sample and were performed using the last observation carried forward procedure. General linear model repeated measures analysis was used in order to assess the effect of time × treatment interaction, considering the treatment group (saffron versus memantine) as the between-subject factor and the study measurements as the within-subject variables (time). If Mauchly's test of sphericity was significant, Greenhouse–Geisser correction for degrees of freedom was used. The mean score change from baseline to the study endpoint on SCIRS, FAST, and MMSE was also compared between the two groups using independent samples T test. Cohen's d effect sizes were determined by dividing the mean difference of the

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two groups by their pooled standard deviation. The frequency of side effects and the number of patients who remained stable throughout this study was compared between two trial groups using chi-square test. A p-value of <0.05 was considered statistically significant.

RESULTS

Participants

One hundred and fourteen individuals were screened for the eligibility criteria, and 68 patients were randomized into two groups. One patient in each group died during the period of this trial because of reasons not related to the research project, and a total number of 60 patients (saffron = 30 and memantine = 30) completed the trial (Figure 1). Because all dropouts occurred after the second visit and all patients had at least one post-baseline assessment, their data were analyzed using last observation carried forward procedure. There were no significant differences between the two groups regarding demographic characteristics of the participants as well as their baseline scores on the study measurements (Table 1). The patients' past medical history, prior medications use, and their baseline laboratory tests are summarized in Table 2. All patients could tolerate and were treated with the planned doses of medications (20 and 30 mg/day for memantine and saffron, respectively) until the end of trial.

Table 1. Baseline data of the patients in both study groups

Variable	Saffron group	Memantine group	p-value
Age, years, mean (SD)	77.73 (8.05)	77.47 (7.99)	0.82
Duration of illness, years, mean (SD)	4.26 (1.44)	4.44 (1.43)	0.61
Education, years, mean (SD)	5.88 (4.63)	5.91 (4.84)	0.98
Gender, *n*			
Female	13	16	0.62
Male	21	18	
Weight, kg, mean (SD)	63.4 (11.8)	62.6 (12.5)	0.47
Marital status, *n*			
Married	19	17	0.75
Divorced	2	1	
Widow	13	16	
Baseline scores, mean (SD)			
SCIRS	20.76 (1.59)	20.47 (1.69)	0.46
FAST	2.97 (0.96)	3.05 (1.01)	0.71
MMSE	11.23 (1.92)	11.11 (1.53)	0.78

SCIRS, Severe Cognitive Impairment Rating Scale; FAST, Functional Assessment Staging; MMSE, Mini-Mental State Examination.

Outcomes

Baseline scores were not significantly different between the two groups on SCIRS [MD(95%CI) = 0.29

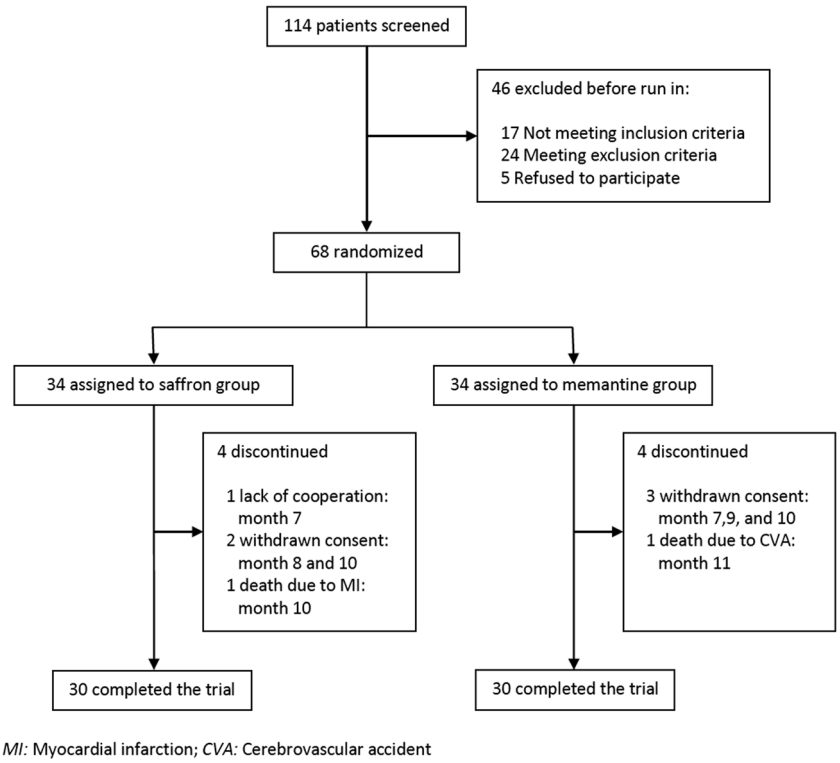

Figure 1. Flow diagram of the study

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Table 2. Clinical characteristics of the patients in both study groups

Variable	Saffron group	Memantine group
Past medical history, *n*		
HTN	19	15
HLP	16	21
DM	4	6
CAD	14	13
Past drug history, *n*		
No drugs	5	3
Donepezil	16	16
Rivatigmine	10	14
Donepezil + rivatigmine	3	—
Donepezil + rivastigmine + galantamine	—	1
Baseline lab data, mean (SD)		
WBC, $\times 10^9$/L	5.24 (1.0)	5.30 (1.2)
RBC, $\times 10^{12}$/L	4.79 (0.3)	4.75 (0.3)
Hb, g/L	15.09 (1.8)	14.75 (1.6)
BUN, mg/dL	17.8 (3.3)	17.3 (3.6)
Triglycerides, mg/dL	142 (81.5)	144 (83.8)
Total cholesterol, mg/dL	202 (26.3)	200 (24.1)
LDL, mg/dL	125 (26.5)	126 (27.2)
HDL, mg/dL	50 (11.9)	51 (13.3)
AST, U/L	20.3 (3.6)	20.1 (3.4)
ALT, U/L	18.3 (4.7)	18.4 (4.4)

HTN, hypertension; HLP, hyperlipidemia; DM, diabetes mellitus; CAD, coronary artery disease; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; BUN: blood urea nitrogen; LDL, low density lipoprotein; HDL, high density lipoprotein; AST, aspartate transaminase; ALT, alanine transaminase.

(−0.50 to 1.09), $t(66) = 0.73$, $p = 0.46$], FAST [MD (95%CI) = −0.08 (−0.56 to 0.39), $t(66) = -0.36$, $p = 0.71$], or MMSE [MD(95%CI) = 0.11 (−0.72 to 0.95), $t(66) = 0.27$, $p = 0.78$]. As the primary outcome measure, repeated measures analysis did not show significant effect for time × treatment interaction on SCIRS scores [$F(2.95, 194.78) = 2.25$, $p = 0.08$] indicating that both groups had a similar behavior across time in this study (Figure 2). During the 1-year follow-up period of this trial, saffron-treated patients experienced 9.18% (5.34) decrease in the SCIRS scores compared with 7.79% (6.48) decrease experienced by the memantine group. Sixteen patients in the saffron group and 19 ones in the memantine group remained stable (≤10% change in SCIRS scores from baseline to the endpoint), a difference that was not statistically significant ($\chi^2(1) = 0.46$, $p = 0.62$). On the basis of the baseline FAST scores, all of the participants were functionally suffering from moderate to severe stage of the disease (stage 6). Comparing the final FAST scores (month 12) with the baseline ones, 19% of patients ($n = 13$; saffron: 9, memantine: 4) remained functionally stable during the course of this trial, and the FAST stage of three patients (saffron: 2, memantine: 1) was improved by one level. By the study endpoint, 53% ($n = 36$; saffron: 22, memantine: 14) and 24% ($n = 16$; saffron: 6, memantine: 10) of the participants experienced deterioration of their FAST stage by one and two levels, respectively. Independent samples *T* test demonstrated no significant differences between saffron-treated and memantine-treated patients in the change of SCIRS, FAST, and MMSE scores from baseline to the final visit (Table 3).

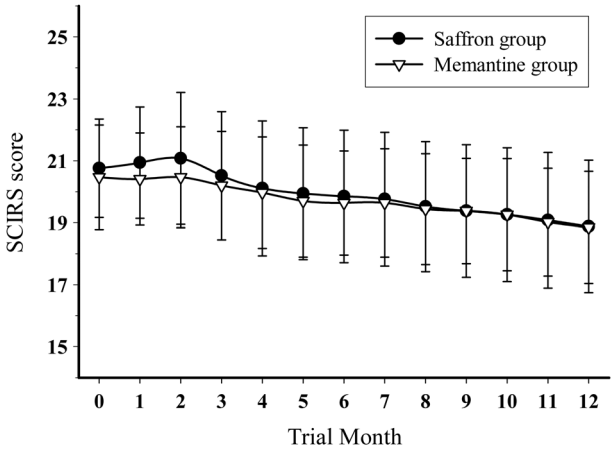

Figure 2. Comparison of Severe Cognitive Impairment Rating Scale scores changes [mean (SEM)] over time between the two study groups

Clinical complications and adverse events

Patients' vital signs, laboratory tests, and electrocardiography did not change significantly from baseline to the final visit. On the basis of the AEs checklist, a total number of seven side effects were reported during this trial, which were all mild and resolved spontaneously without any intervention. No significant difference was detected between the two groups in the frequency of these AEs (Table 4).

DISCUSSION

The results of this trial showed that the efficacy of saffron can be compared with memantine in reducing the cognitive deterioration in patients suffering from moderate to severe AD. Although memantine-treated patients experienced less cognitive decline than the saffron group (7.79% vs. 9.18% decrease in SCIRS scores), this difference was not statistically significant, and repeated measures analysis revealed that both groups had a similar behavior during the 1-year period of this study. The goal of treatment in patients with severe AD is to stabilize or at least slow the rate of their cognitive decline. The number of patients who remained cognitively stable throughout this trial was not significantly different between the two groups. Although evaluated in a relatively short period, we observed a similar performance from both groups in the ability of accomplishing their

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Table 3. Comparison of score changes from baseline (month 0) to the endpoint (month 12) between the two groups on different study measures

Measurement	Saffron group, mean (SD)	Memantine group, mean (SD)	Mean difference (95%CI)	$t(66)$	p-value	Cohen's d
SCIRS	1.88 (1.14)	1.61 (1.34)	0.26 (−0.34 to 0.87)	0.87	0.38	0.21
FAST	0.94 (0.73)	0.97 (0.83)	−0.02 (−0.41 to 0.35)	−0.15	0.87	−0.03
MMSE	1.29 (1.36)	1.67 (1.57)	−0.38 (−1.09 to 0.32)	−1.07	0.28	−0.25

SCIRS, Severe Cognitive Impairment Rating Scale; FAST, Functional Assessment Staging; MMSE, Mini-Mental State Examination.

Table 4. Frequency of adverse events in the two study groups

Adverse event	Saffron group	Memantine group	p-value
Nausea and vomiting, *n*	8	6	0.76
Dry mouth, *n*	4	4	1.00
Fatigue, *n*	4	5	1.00
Dizziness, *n*	4	6	0.73
Confusion, *n*	1	1	1.00
Agitation, *n*	—	2	1.00
Sedation, *n*	1	3	0.61

daily activities as assessed by the FAST scale. The results of saffron treatment in this study are particularly encouraging in light of serious limitations, which exist in treatment options for patients affected by advanced stages of AD. Memantine, donepezil, or their combination therapy are the only approved pharmacological choices with proven efficacy in moderate to severe AD, yet a large number of patients do not respond optimally to these agents and may discontinue them because of unfavorable side effects (Herrmann and Gauthier, 2008; Hsiung and Feldman, 2008).

To the best of our knowledge, this is the first trial evaluating the efficacy and safety of saffron in patients suffering from moderate to severe AD. The outcomes of this study are in line with previous reports of saffron efficacy in milder stages of the disease. Encouraging results of saffron therapy compared with placebo and donepezil have been reported for AD in two short-term clinical trials (Akhondzadeh *et al*., 2010a, 2010b); however, some fundamental differences exist between the present study and the previous ones. As an inclusion criterion, we only recruited the participants who were suffering from more severe stages of AD (baseline MMSE score: 8–14) and tried to compare the efficacy of saffron with memantine in this category of patients. We applied SCIRS as the efficacy assessment measure because this scale is more specialized for evaluating cognitive functions in severely demented patients compared with AD assessment scale-cognitive subscale and clinical dementia rating scale, which were applied in the two previous trials. The present study also benefits from a larger sample size, more follow-up visits, and a prolonged period for evaluating the medications effects.

In addition to cognitive improvement, patients with AD may also benefit from some other aspects of treatment with saffron, a point that can be considered as a clinical justification for its use. Although extremely disabling, the management of associated neuropsychiatric disturbances is commonly overlooked in patients with AD (Ballard *et al*., 2008). Depression is one of the most frequent and challenging comorbidities of AD with serious negative impacts on the patients' quality of life as well as their long-term prognosis. Up to 50% of patients with AD have depression, and it has been suggested that treating depressive symptoms in these patients would improve their cognitive performance in addition to its other obvious benefits (Lee and Lyketsos, 2003). Interestingly, antidepressant properties of saffron compounds have been evidenced in different clinical trials suggesting more advantages for this agent in improving some of the neuropsychiatric symptoms associated with AD (Akhondzadeh *et al*., 2004; Akhondzadeh *et al*., 2005; Noorbala *et al*., 2005; Moshiri *et al*., 2006; Akhondzadeh Basti *et al*., 2007). However, the efficacy of saffron for treating depression in this specific group of patients has not been studied yet and can be the subject of a future research. The common mechanism by which saffron and memantine reduce cognitive deterioration in severely demented patients is proposed to be their inhibitory effect on glutamate excitotoxicity and neuronal death, a devastating process that plays a principal role in AD pathogenesis (Riederer and Hoyer, 2006; Revett *et al*., 2013). Both agents act as NMDA receptor antagonists and have been shown to decrease extracellular glutamate levels as well (Hosseinzadeh *et al*., 2008; Berger *et al*., 2011; Ohno *et al*., 2012). Furthermore, saffron constituents have relatively inhibitory effects on acetylcholinesterase and consequently increase the synaptic acetylcholine levels (Geromichalos *et al*., 2012), a pathway that is in common with the other important category of anti-AD medications (ACEIs). In addition to its modulatory effects on neurotransmitter systems, saffron interacts with the main pathology of AD by inhibiting Aβ peptides fibrillization and amyloid plaques formation (Papandreou *et al*., 2006; Ahn *et al*., 2011).

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Antioxidant and radical scavenging properties of saffron are well studied and may be another mechanism underlying its cognitive-enhancing effects (Montoro *et al*., 2012; Serrano-Diaz *et al*., 2012).

In terms of safety, no significant difference was detected between the two groups in the frequency of AEs during the course of this short-term trial. It should be noted that no causality assessment was performed in this study and the undesired effects were just recorded and compared between the two groups. Although this study was relatively short in order to make an absolute comparison between probable side effects of these two medications, according to the present evidences, saffron is likely to show lower rates of AEs compared with memantine in long-term use, a point that should be further clarified in the future trials. A small number of AEs have been reported after high dose administration of saffron in laboratory studies, but the therapeutic doses of this agent are generally known to be safe in clinical practice (Schmidt *et al*., 2007; Modaghegh *et al*., 2008). To the best of our knowledge, no serious AE has been reported in well-designed clinical trials of saffron to date that can be considered as an advantage of this agent compared with the currently available medications (Ulbricht *et al*., 2011). Because most of the patients with severe AD are in old ages, cardiovascular AEs are a major concern in planning their pharmacotherapy regimen. Saffron not only is safe with regard to the cardiovascular system but also has some beneficial cardioprotective properties such as improving the lipid profile, decreasing the blood pressure, and inhibiting atherosclerotic plaques formation (Kamalipour and Akhondzadeh, 2011). However, the outcomes of this study should be interpreted with caution in light of its methodological limitations. The small sample size and lack of a placebo arm were the most prominent limitations of this trial. We did not have a placebo arm because it was unethical to inhibit severely demented patients from receiving an effective treatment and we could not test this medication in a very large sample size because this was the first trial in this specific population. Therefore, this study should be considered as a pilot one for further investigations with larger sample sizes and better designs. Although we followed up the participants for 1 year, this period is relatively short to judge about the long-term benefits of saffron on the patients' functional and cognitive performance. Finally, we did not apply any specific scale in this study in order to evaluate the probable benefits of saffron in improving the associated behavioral and psychiatric symptoms of AD.

CONCLUSION

In conclusion, 1-year treatment with saffron was comparable with memantine for reducing cognitive deterioration in patients suffering from moderate to severe AD. Nevertheless, long-term efficacy and safety of saffron as well as its optimal dosing and administration strategy require further investigations.

CONFLICT OF INTEREST

No conflict of interest exists for any of the authors associated with the manuscript, and there was no source of extra-institutional commercial funding. The funding organization had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript and the decision to submit the paper for publication.

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