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ORIGINAL ARTICLE

Saffron in the treatment of patients with mild to moderate Alzheimer's disease: a 16-week, randomized and placebo-controlled trial

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ABSTRACT

What is known: **Herbal medicines have been used in the treatment of behavioural and psychological symptoms of dementia but with variable response. *Crocus sativus* (saffron) may inhibit the aggregation and deposition of amyloid β in the human brain and may therefore be useful in Alzheimer's disease (AD).**

Objective: **The goal of this study was to assess the efficacy of saffron in the treatment of mild to moderate AD.**

Methods: **Forty-six patients with probable AD were screened for a 16-week, double-blind study of parallel groups of patients with mild to moderate AD. The psychometric measures, which included AD assessment scale-cognitive subscale (ADAS-cog), and clinical dementia rating scale-sums of boxes, were performed to monitor the global cognitive and clinical profiles of the patients. Patients were randomly assigned to receive capsule saffron 30 mg/day (15 mg twice per day) (Group A) or capsule placebo (two capsules per day) for a 16-week study.**

Results: **After 16 weeks, saffron produced a significantly better outcome on cognitive function than placebo (ADAS-cog: $F = 4{\cdot}12$, d.f. = 1, $P = 0{\cdot}04$; CDR: $F = 4{\cdot}12$, d.f. = 1, $P = 0{\cdot}04$). There were no significant differences in the two groups in terms of observed adverse events.**

What is new and conclusion: **This double-blind, placebo-controlled study suggests that at least in the short-term, saffron is both safe and effective in mild to moderate AD. Larger confirmatory randomized controlled trials are called for.**

***Keywords*: Alzheimer's disease, clinical trial, saffron**

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INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia in the elderly (1). The onset of the disease is insidious, generally occurring after the age of 55 years and increasing in incidence with advancing age. The average risk of developing AD is approximately 5% at age 65 years and subsequently increasing 2-fold every 5 years. The clinical course is marked by a gradual deterioration of intellectual function, a decline in the ability to accomplish routine activities of daily living, and enduring changes in personality and behaviour (1, 2). One of the hallmarks of pathology of AD is the presence of numerous amyloid plaques in the cerebral cortex (3). The major component of amyloid plaques is amyloid β, which is derived from the amyloid precursor protein (APP). APP is pres-

ent in the brain and peripheral tissues (4, 5). The treatments of choice in AD are cholinesterase inhibitors and NMDA-receptor antagonists, although doubts remain about the therapeutic effectiveness of these drugs (6). Herbal medicines are being used by about 80% of the world population primarily in the developing countries for primary health care (7, 8). The growth in the popularity of alternative approaches to health care has led to an interest in the treatment of dementia through herbal remedies which may be cognition-enhancing (6). Indeed, herbal medicines have been used in the treatment of behavioural and psychological symptoms of dementia but with variable response (9). Some plant species, which have been used in traditional medicine, for this effect, have a historically demonstrable lack of toxicity (6). There is now an increase in studies investigating the action of the extracts of some of these plants. Of particular interest are those which are thought to have an action similar to the approved drugs, or an action which may be linked to what is known or believed about AD and vascular dementia (6).

Ginkgo biloba is an herbal medicine that has been used to treat a variety of ailments for thousands of years in China. An extract of *G. biloba* has been found in several studies to improve the symptoms and slow the progression of AD (10). It has been reported that *Melissa officinalis* (lemon balm) and *Salvia officinalis* (sage) improve cognitive function and reduces agitation in patients with mild to moderate AD (11, 12). *Crocus sativus* L., commonly known as saffron, is used in folk medicine as an antispasmodic, eupeptic, gingival sedative, anticatarrhal, nerve sedative, carminative, diaphoteric, expectorant, stimulant, stomachic and aphrodisiac (6, 13). Furthermore, it has been reported that saffron extract or its active constituents have anticonvulsant, antidepressant, anti-inflammatory, and antitumour effects, and acts as a radical scavenger and improves learning and memory as well as promote the diffusivity of oxygen in different tissues (6, 13). Saffron extract also has chemopreventive and showed protective effects on genotoxin-induced oxidative stress in Swiss albino mice (13). Recently, a number of clinical trials have shown that this herb is as effective as fluoxetine and imipramine in the treatment of mild to moderate depression (14–16). Three main chemical compounds have been identified in saffron: carotinoids which give it the bright red colouring; picrocrocin, which gives the spice its characteristic bitter taste and safranal, which provides the spicy aroma. The carotenoid pigments consist of crocetin di-(b-D-glucose)-ester, crocetin-(b-D-gentiobiosyl)-(b-D-glucosyl)-ester and crocetin-di-(b-D-digentiobiosyl)-ester(crocin). Crocin is the actual active component involved in both the improvement of learning and memory and preventive effect of long-term potentiation (LTP) blocked by ethanol *in vivo* (13). It has been also reported that crocin selectively antagonizes the inhibitory effect of ethanol on NMDA receptor-mediated responses in hippocampal neurons (17). This action of crocin may underlie the antagonism against ethanol-induced memory impairment (18). Thus, crocin can be used as a new pharmacological tool for studying the mechanism of ethanol inhibition of NMDA receptor activities (17). Therefore, it can be concluded that crocin may have potential for treating neurodegenerative damage induced by oxidative stress (19, 20). A recent study also showed that *C. sativus* has antioxidant and anti-amyloidogenic activity, thus reinforcing ethnopharmacological observations that *C. sativus* had a positive effect on cognitive function (21). This study suggested that *C. sativus* might inhibit the aggregation and deposition of amyloid β in the human brain (21).

Iran as the world's largest producer of saffron has considerable knowledge in the use of this traditional herbal medicine. But, unfortunately, Iran has not been able to capitalize on this wealth of information and promote the use of saffron in the developed world despite the world-wide renewed interest in herbal medicines (6). This may be due to inadequate evidence despite the increasing evidence from Persian traditional medicine as well as recent basic research that saffron may be useful for treating AD (18, 21–24). Our objective was to assess the efficacy of *C. sativus* in the treatment of mild to moderate AD, using a double-blind, randomized, placebo-controlled trial design.

METHODS

Setting

This trial was a 16-week, double-blind study of parallel groups of patients with mild to moderate

AD and was undertaken at three sites in Iran from January 2006 to January 2009.

Participants

Forty-six patients with probable AD of mild to moderate severity were screened for study entry. Diagnosis of AD was established according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, 4th edition (25). The subjects were classified with probable AD status according to the criteria of the National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (26). Patients had to provide computed tomography or magnetic resonance imaging scans, performed within one year before or at the screening, for this study to demonstrate absence of clinically significant multi-infarct dementia or active cerebrovascular disease. The inclusion criteria were age older than 55 years and baseline mini-mental state examination (MMSE) score of 15–26 (inclusive) (27). Patients with AD who may also have cerebrovascular disease as evidenced by risk factors such as hypertension, elevated cholesterol levels, diabetes and smoking, but in stable condition, were also eligible to enter into the study. The patients also had to have a knowledgeable and reliable caregiver to accompany the participant to all trial visits and supervise administration of the trial medication as one of the inclusion criteria. Patients were excluded if they had evidence of cardiovascular disease that was likely to interfere with study participation and completion, or if they had any other neurodegenerative disorders. Additional exclusion criteria included any clinically significant psychiatric, hepatic, renal, pulmonary, metabolic or endocrine conditions; urinary outflow obstruction or active peptic ulcer or a history of epilepsy or significant drug or alcohol abuse. Patients were also excluded from the study if they had received cholinomimetic therapy for AD within the preceding 60 days and earlier discontinuation was not solely for the purpose of study enrollment. Any other antidementia medication (e.g., chronic non-steroidal anti-inflammatory drugs, selegiline or estrogen) also had to be discontinued before study entry. Drugs with a psychotropic action were discontinued 48 h before cognitive evaluation. The protocol was approved by the Institutional Review Board (IRB) of Tehran University of Medical Sciences (Grant No. 4843). The patients and their legally authorized representative provided informed consent in accordance with the procedures outlined by the local IRB, and were informed that they could withdraw from trial at any time. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions (28).

Measurements

The psychometric measures, which included the MMSE, AD Assessment Scale-cognitive subscale (ADAS-cog) (29), and clinical dementia rating scale–sums of boxes (CDR-SB) (30), were performed to monitor the global cognitive and clinical profiles of the subjects. All measures were administered at baseline and every 2 weeks after the treatment started.

Intervention

Patients were randomized to receive capsule of saffron or capsule of placebo in a 1 : 1 ratio using a computer-generated code to receive a twice-daily capsule of saffron or a capsule of placebo. No individual participant randomization code was revealed during the trial. Treatment codes were unblinded at the termination of the study after the database was locked. Placebo and saffron capsules were visually identical. In this double-blind, multicenter trial, patients were randomly assigned to receive capsule saffron 30 mg/day (15 mg twice per day) (Group A) or capsule of placebo (two capsules per day) for a 16-week study.

Preparation of capsule of saffron

The saffron used in this study was donated by Green Plants of Life Co (IMPIRAN, Tehran, Iran) and was identified by the Department of Cultivation and Development of Institute of Medicinal Plants, Tehran, Iran. The extract of stigmas was prepared as follows: 120 *g* of dried and milled stigmas 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 extract was standardized by safranal and crocin. The likely most therapeutically important compounds in saffron are crocin, picocrocin and safranal. The amounts of these main compounds can be used to express the quality of saffron. The extract was standardized by safranal and crocin contents. Drug samples are evaluated by a safranal and crocin value by means of a spectrophotometric method. Safranal and crocin value are expressed as direct reading of the absorbance at about 330 nm and 440 nm, respectively. Each capsule had 0·13–0·15 mg safranal and 1·65–1·75 mg crocin.

Safety evaluation

All adverse events, reported or observed, were recorded at each visit. Routine physical examinations were conducted at each visit. Complete physical examinations, including 12 lead ECG recordings, were conducted at week 0, week 8, and week 16.

Statistical analysis

The primary efficacy analysis was done with data from the intention-to-treat population with the last observation carried forward procedure, defined as all patients randomly assigned to treatment who received at least one dose of study drug. A two-way repeated measures analysis of variance (time–treatment interaction) was used. We considered the two groups as the between-subjects factor (group) and the nine measurements during treatment as the within-subjects factor (time). This was done for both ADAS-cog and CDR-SB scores. To compare the reduction in score of the ADAS-cog and CDR-SB scales at week 16 in relation to baseline, an unpaired two sided Student's *t*-test was used. Fisher's exact test was employed to compare the baseline data and frequency of adverse events between the protocols. Results are presented as mean (SEM) and were considered significant at a *P*-value of <0·05.

RESULTS

Figure 1 shows the trial profile. From January 2006 to June 2008, 82 patients were screened for the trial, of whom 46 were randomized to either saffron or placebo capsule. The last patient completed the study in January 2009. There was no difference in baseline characteristics including, gender, age, duration of illness and education level (Table 1). In the saffron and placebo group the number of dropouts was 1, and 3, respectively.

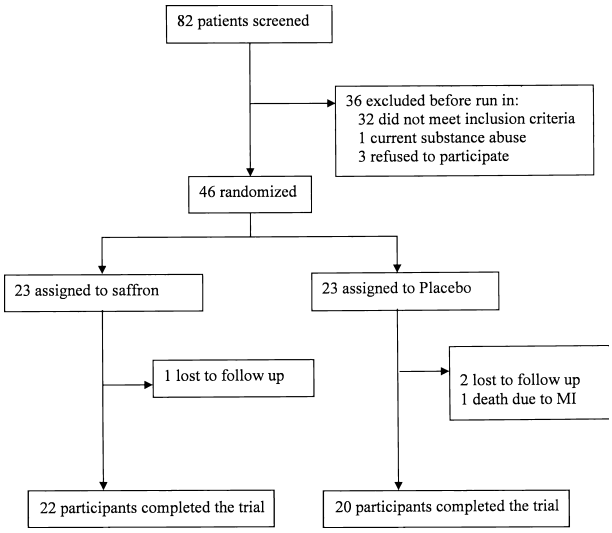

Fig. 1. Trial profile.

Efficacy measures

ADAS-cog. The mean ± SEM scores of the two groups of participants are presented in Fig. 2. There were no significant differences between the two groups at week 0 (baseline) on the ADAS-cog rating scale (t = 0·07, d.f. = 44, P = 0·94). The difference between the two groups was significant as indicated by the effect of group, the between-subjects factor (F = 4·12, d.f. = 1, P = 0·04). The behaviour of the two treatments was not similar over the trial period (groups-by-time interaction, Greenhouse–Geisser correction; F = 204·43, d.f. = 3·63, P < 0·0001). The difference between the two groups was significant at week 16 (endpoint) (t = 4·16, d.f. = 44, P < 0·0001). The changes at week 16 compared to baseline were: −3·69 ± 1·69 (mean ± SD) and 4·08 ± 1·34 for saffron and placebo, respectively. A significant difference was observed on the change of scores of the ADAS-cog rating scale at week 16 compared with week 0 in the two groups (t = 17·27, d.f. = 44, P < 0·0001).

CDR-SB. The mean ± SEM scores of two groups of participants are presented in Fig. 3. There were no significant differences between the two groups

Table 1. Baseline data

	Saffron group	Placebo group	*P*
Gender	Male: 13, female: 10	Male: 12, female: 11	ns
Age (mean ± SD)	72·65 ± 3·89 (year)	73·13·53 ± 4·70 (year)	ns
Level of education	Under diploma: 12, diploma: 8, higher diploma: 3	Under diploma: 13, diploma: 7, higher diploma: 3	ns
Time since diagnosis (mean ± SD)	20·30 ± 9·21(month)	19·17 ± 7·42(month)	ns

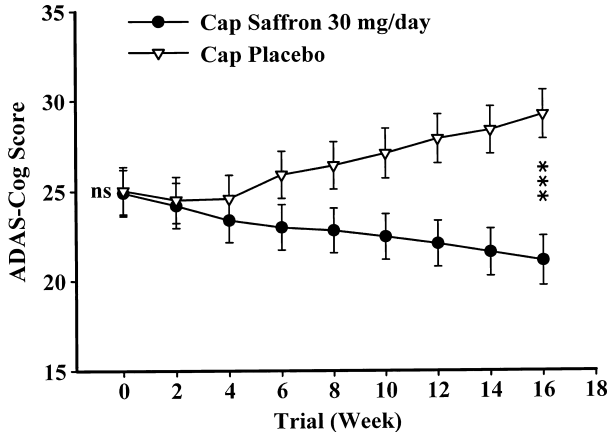

Fig. 2. Mean ± SEM scores of the two protocols on the ADAS-cog score. ns, non-significant.

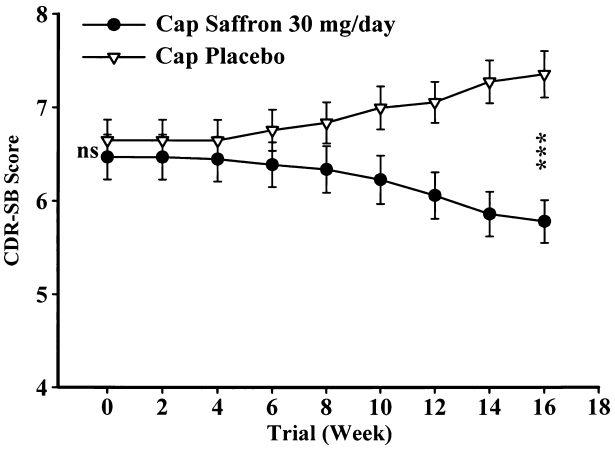

Fig. 3. Mean ± SEM scores of the two protocols on the CDR-SB score. ns, non-significant.

at week 0 (baseline) on the CDR-SB (t = 0·52, d.f. = 44, P = 0·60). The difference between the two groups was significant as indicated by the effect of group, the between-subjects factor (F = 4·12, d.f. = 1, P = 0·04). The behaviour of the two treatments was not similar over the trial period (groups-by-time interaction, Greenhouse–Geisser correction; F = 115·19, d.f. = 4·48, P < 0·0001). The difference between the two groups was significant at week 16 (endpoint) (t = 4·55, d.f. = 44, P < 0·0001). The changes at week 16 compared with baseline were: −0·67 ± 0·24 (mean ± SD) and 0·63 ± 0·45 for saffron and placebo, respectively. A significant difference was observed on the change of scores of the CDR-SB at week 16 compared with week 0 in the two groups (t = 12·06, d.f. = 44, P < 0·0001).

Table 2. Number of patients with adverse events

Adverse events	Saffron (%)	Placebo (%)	*P*
Dizziness	2 (8·69)	3 (13·04)	1·00
Dry mouth	3 (13·04)	1 (4·34)	0·60
Fatigue	1 (4·34)	2 (8·69)	1·00
Hypomania	2 (8·69)	0	0·48
Nausea	2 (8·69)	1 (4·34)	0·25

Safety

There was one death in the placebo group because of myocardial infarction. Five adverse events were observed over the study. The difference between the saffron and placebo in the frequency of adverse events was not significant (Table 2). None of adverse events was severe or caused a drop-out.

DISCUSSION

Alzheimer's disease, a major public health problem, is debilitating for patients and profoundly affects the lives of their caregivers and loved ones adversely

(1, 4). Considerable effort has therefore been devoted to developing new and effective treatments. Treatment strategies for AD include a variety on interventions directed at multiple targets. The available approved medications for AD are often unsatisfactory, and there may be a place for alternative medicines, in particular herbal medicine (6).

Herbal medicine are still the mainstay of therapy for approximately 75–80% of the world population, mainly in the developing countries, in primary health care because of better cultural acceptability, and often better side-effects profiles. However, during the last decade there has been a major increase in their use in the developed world (31). This study indicates that the saffron extract is useful for the treatment of patients with mild to moderate AD as shown by improvements in both the ADAS-cog and CDR-SB measures. This is the first study to evaluate saffron extract in the treatment of patients with mild to moderate AD and so it is not possible to draw any comparisons with the results of other trials. Nevertheless, there is increasing scientific evidence to suggest that saffron may be useful in the management of AD (18, 21–24).

These studies showed that oral saffron extract improved the memory of mice predamaged with ethanol and that crocin prevents the inhibitory effects of ethanol on LTP in mice (18, 21–24). Low doses of saffron antagonized the extinction of recognition memory in the object recognition test and counteracted the scopolamine-induced performance deficits in the passive avoidance task (18). The results of this trial are consistent with the results of those basic studies (18, 21–24) as well as the reported antioxidant and antiamyloidogenic activity of an extract of saffron stigmas (21).

Behavioural symptoms are common in AD and are a major contributor to disease morbidity (32). In AD, depression has been associated with more rapid cognitive decline, increased caregiver burden, increases in cost of patient-care as a result of earlier institutionalization, greater use of medication, more frequent adverse side-effects and more extensive institutional staffing needs (32). Interestingly several basic studies and recent published clinical trials have shown that saffron may be antidepressant (14–16, 33), with frequency of adverse events being was similar to that seen in placebo groups. In our study, adverse events were generally mild to moderate with no dropout as a result of adverse events.

The limitations of present study include the small number of patients and a relatively short period of follow-up. Therefore, further randomized controlled evaluation should be undertaken. The use of herbal medicines in the treatment of AD should be compared with the pharmacological treatment currently in use. Therefore, comparison with anticholinestrase inhibitors such as donepezil would be interesting.

CONCLUSIONS

This study indicates that at least in the short-term saffron is safe and effective in mild to moderate AD. Larger and longer randomized controlled studies are required to further validate this herbal remedy.

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