

A 22-week, multicenter, randomized, double-blind controlled trial of *Crocus sativus* in the treatment of mild-to-moderate Alzheimer's disease

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Abstract

Rationale There is increasing evidence to suggest the possible efficacy of *Crocus sativus* (saffron) in the management of Alzheimer's disease (AD).

Objective The purpose of the present investigation was to assess the efficacy of *C. sativus* in the treatment of patients with mild-to-moderate AD.

Methods Fifty-four Persian-speaking adults 55 years of age or older who were living in the community were eligible to participate in a 22-week, double-blind study of parallel

groups of patients with AD. The main efficacy measures were the change in the Alzheimer's Disease Assessment Scale—cognitive subscale and Clinical Dementia Rating Scale—Sums of Boxes scores compared with baseline. Adverse events (AEs) were systematically recorded. Participants were randomly assigned to receive a capsule saffron 30 mg/day (15 mg twice per day) or donepezil 10 mg/day (5 mg twice per day).

Results Saffron at this dose was found to be effective similar to donepezil in the treatment of mild-to-moderate AD after 22 weeks. The frequency of AEs was similar between saffron extract and donepezil groups with the exception of vomiting, which occurred significantly more frequently in the donepezil group.

Conclusion This phase II study provides preliminary evidence of a possible therapeutic effect of saffron extract in the treatment of patients with mild-to-moderate Alzheimer's disease. This trial is registered with the Iranian Clinical Trials Registry (IRCT138711051556N1).

Keywords Cholinesterase inhibitors · *Crocus sativus* · Clinical trial · Dementia

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Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly (Tedeschi et al. 2008). This condition is characterized by a progressive loss of memory, deterioration of virtually all intellectual functions, increased apathy, decreased speech function, disorientation, and gait irregularities. AD is the most widely known of the degenerative

diseases (Citron 2004). It is a condition that is commonly associated with considerable psychological and emotional distress for patients and their families. It is estimated that 3.5% of the population in the USA between the ages of 65 and 74 years of age is in at least the initial stage of AD (Citron 2004; Tedeschi et al. 2008). Advancing age is the most common risk factor for so-called AD with a doubling of risk every 5 years after the age of 65. Females are slightly more likely than males to develop Alzheimer's disease (Citron 2004; Tedeschi et al. 2008). Deposition of amyloid- β (A β) in the brain is a neuropathological hallmark of AD and a potential cause of neuronal damage (Golde 2005). Although a "magic bullet" for AD has clearly not as yet been found, certain medicines offer modest benefit, and these may be conveniently divided into three classes, according to whether they may prevent the development of the disease, retard its progression once it has set in, or offer some symptomatic relief (Becker and Greig 2008; Rafii and Aisen 2009). The cholinergic hypothesis of AD is based on the decrease in the cholinergic neurotransmission observed in the central cortex and other areas of the brain (Tsuno 2009). The acetylcholinesterase inhibitors such as donepezil, which can increase intrasynaptic cholinergic activity by inhibiting the degradation of acetylcholine, are the drugs that have demonstrated in many clinical trials beneficial effects on standard measures of cognitive function patients with mild, moderate, or severe AD (Tsuno 2009). New studies suggest novel strategies for AD therapy. The most viable of these at the moment is targeting the disruption of neurotransmitter systems. Counteracting overproduction of amyloid- β is attractive in theory and has spurred the development of secretase inhibitors as well as active and passive immunization techniques. Nevertheless, the present drugs' effects are quite limited (Becker and Greig 2008; Rafii and Aisen 2009).

Herbal medicine is still the mainstay of about 75–80% of the world population, mainly in the developing countries, for primary health care because of better cultural acceptability, better compatibility with the human body, and lesser side effects (Ernst 2006). However, the last decade has seen a major increase in their use in the developed world (Mantle et al. 2002; Izzo and Capasso 2006). Preliminary clinical evidence indicates that some herbal medicines can ameliorate learning and memory in patients suffering from mild-to-moderate AD (Wake et al. 2000; Akhondzadeh and Abbasi 2006). Potential beneficial actions exerted by the active ingredients of these herbs are not limited to the inhibition of cholinesterase inhibitors and include the modification of A β processing, protection against apoptosis and oxidative stress, and anti-inflammatory effects (Wake et al. 2000; Akhondzadeh and Abbasi 2006). *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 (Birks et al. 2009). However, this Cochrane review concluded that the evidence that *G. biloba* has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable (Birks et al. 2009). It has been reported that *Salvia officinalis* and *Melissa officinalis* improve cognitive function and reduce agitation in patients with mild-to-moderate AD (Akhondzadeh et al. 2003a, b).

Saffron is the world's most expensive spice and apart from its traditional value as a food additive, recent studies indicate its potential as an anticancer agent and memory enhancer (Abe and Saito 2000; Abdullaev and Espinosa-Aguirre 2004). The value of saffron (dried stigmas (the top of the center part of a flower that receives the pollen which allows it to form new seeds) of *Crocus sativus* L.) is determined by the existence of three main secondary metabolites: crocin and its derivatives which are responsible for color; picrocrocin which is responsible for taste; and safranal which is responsible for odor (Schmidt et al. 2007). This plant belongs to the Iridaceae family, and as a therapeutically plant, saffron is considered an excellent aid for stomach ailments and an antispasmodic that helps digestion and increases appetite. It also relieves renal colic, reduces stomach ache, and relieves tension (Akhondzadeh and Abbasi 2006; Schmidt et al. 2007). The world's total annual saffron production is estimated at 205 tons/year, with >80% of this harvest originating from Iran, mainly from the South Khorassan province. Saffron is used for depression and dementia in Persian traditional medicine (Akhondzadeh 2007). Indeed, it is a Persian herb with a history as long as the Persian Empire itself (Akhondzadeh et al. 2005; Akhondzadeh Basti et al. 2007). It has been shown that administration of extracts of *C. sativus* L. antagonized ethanol-induced memory impairment in the passive avoidance task in the mouse, and the constituent of saffron extracts, crocin, prevented ethanol-induced inhibition of hippocampal long-term potentiation, a form of activity-dependent synaptic plasticity that may underlie learning and memory (Sugiura et al. 1995a, b; Akhondzadeh 1999). In addition, it has also been reported that crocin counteracted ethanol inhibition of *N*-methyl-D-aspartate receptor-mediated responses in rat hippocampal neurons (Abe et al. 1998). Low doses of *C. sativus* extract antagonized extinction of recognition memory in the object recognition test and scopolamine-induced performance deficits in the passive avoidance task in rat (Pitsikas et al. 2007).

In conclusion, these studies suggest that *C. sativus* stigmas extract may have antioxidant and anti-amyloidogenic activity, thus reinforcing ethnopharmacological observations that saffron has a positive effect on cognitive function (Schmidt et al. 2007). Another study indicated the possible use of *C. sativus* stigma constituents for inhibition of aggregation and deposition of amyloid- β (Papandreou et al. 2006). There-

fore, increasing evidence from Persian traditional medicine as well as recent basic research confirms that saffron may have potential for treating AD. In addition, we have recently reported a double-blind, placebo-controlled study that supports the efficacy of saffron extract for 16 weeks in the treatment of mild-to-moderate Alzheimer's disease (Akhondzadeh et al. 2009). However, the use of herbal medicines in the treatment of AD should be compared with the pharmacological treatment currently in use. Therefore, the purpose of the present investigation was to assess the efficacy of *C. sativus* compared to donepezil in the treatment of patients with mild-to-moderate AD in a 22-week, double-blind, and controlled trial.

Materials and methods

Trial design

This study was a prospective, 22-week, double-blind study of parallel groups of patients with mild-to-moderate Alzheimer's disease and was undertaken in three sites of Iran, from January 2007 to February of 2009.

Participants

Fifty-four Persian-speaking adults 55 years of age or older who were living in the community were eligible to participate. Patients were required to meet the Diagnostic and statistical manual of mental disorders, 4th edition (DSM-IV, text revision) criteria for dementia and the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria for probable AD (Mckhann et al. 1984). Patients also had to have regular contact with a responsible caregiver. Inclusion criteria were mild-to-moderate dementia (Minimal State Examination, MMSE; 15–26 inclusive), 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 scan within 1 year before enrolment (Folstein et al. 1975). Patients were required to be ambulatory and have sufficient hearing and vision to comply with assessments. Previous cholinesterase inhibitor, memantine therapy, ginkgo, or saffron must have been discontinued at least 3 months before randomization and that such discontinuation was not solely for the purpose of study enrolment.

Patients with any of the following conditions were not qualified for the study: known hypersensitivity to cholinesterase inhibitors, active and uncontrolled disease conditions (diabetes, hypertension, thyroid disease, obstructive pulmonary disease, hematologic/oncologic disorders within

past 12 months, active gastrointestinal, renal, hepatic, endocrine, or cardiovascular disease), a current DSM-IV diagnosis of major depressive disorder or any current primary psychiatric diagnosis other than AD and dementia complicated by delirium, or subjects with a history of drug or alcohol abuse within the past 2 years. Sedative-hypnotics and sedative cough and cold remedies were discontinued 48 h before cognitive evaluations whenever possible.

The protocol was approved by the Institutional Review Board (IRB) of Tehran University of Medical Sciences (Grant No. 8480). 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 the experiment at any time. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions.

Measurements

The psychometric measures, which included the MMSE, Alzheimer's Disease Assessment Scale—cognitive subscale (ADAS-cog), and Clinical Dementia Rating Scale—Sums of Boxes (CDR-SB), were performed to monitor the global cognitive and clinical profiles of the subjects (Hughes et al. 1982; Rosen et al. 1984). MMSE was used as screening tool. All measures were administered at baseline and every 2 weeks after the treatment started.

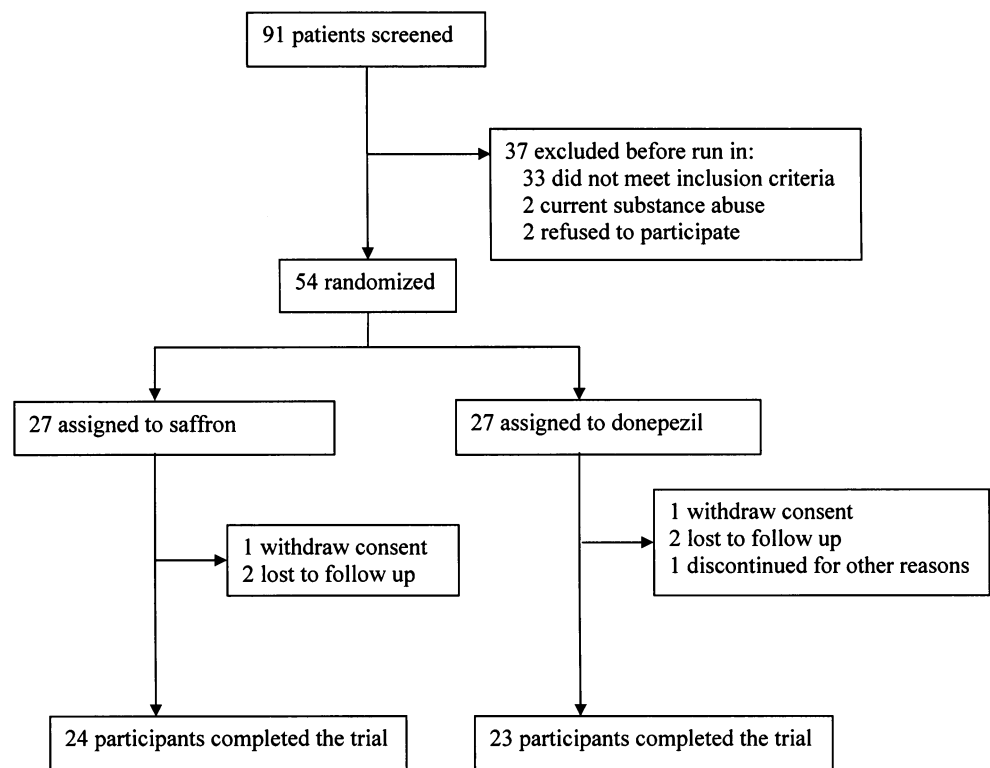
Intervention

The investigator was provided with a sealed randomization code for each available medication number. Blinding was to be broken only if the patient's trial medication would affect specific emergency treatment. All randomization codes, opened or sealed, were retrieved at the end of the study. Patients were randomized to receive capsule of saffron or a capsule of donepezil in a 1:1 ratio using a computer-generated code. Donepezil and saffron capsules were visually identical in terms of shape and color. In this double-blind, multicenter trial, patients were randomly assigned to receive capsule saffron 30 mg/day (15 mg twice per day) or capsule donepezil 10 mg/day (5 mg twice per day; Aricept from Pfizer; group 2) for a 22-week study. Following the screening phase, a capsule of saffron 15 mg or a capsule of donepezil 5 mg was given for the first 4 weeks, after which the dose was increased to two capsules of saffron or donepezil per day for the rest of the trial.

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

Fig. 1 Trial profile



the Department of Cultivation and Development of Institute of Medicinal Plants, Tehran, Iran. The stigma's extract was prepared as follows: 120 g of dried and milled stigmas was extracted with 1,800 ml ethanol (80%) by percolation procedure in three steps 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 most important compounds in saffron are crocin, picrocrocin, and safranal. The amounts of these main compounds can be used to express the quality of saffron. Safranal and crocin can be used as a measure of saffron capsule quality. 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 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 clinic visit. Complete physical examinations, including 12 lead electrocardiogram recordings, were conducted at weeks 0, 8, and 22.

Statistical analysis

Considering a three-point difference in the change in ADAS-cog score between patients treated with saffron and donepezil that clinically is meaningful, we calculated at least 27 patients in each arm. 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 seven measurements during treatment as the within-subjects factor (time). This was done for

Table 1 Characteristics of patients

	Saffron group	Donepezil group	<i>P</i>
Gender (M/F)	14:13	15:12	ns
Age (mean ± SD), years	72.70±6.20	73.85±4.63	ns
Level of education			
Under diploma	16	15	ns
Diploma	7	8	
Higher diploma	4	4	
Time since diagnosis, months	22.33±14.63	21.03±14.19	ns

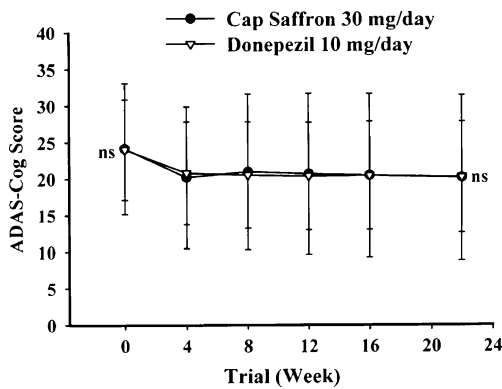


Fig. 2 Mean \pm SD scores of the two protocols on the ADAS-cog score. *ns* nonsignificant

both ADAS-cog and CDR-SB scores. To compare the reduction in score of the ADAS-cog and CDR-SB scales at week 22 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 (standard deviation, SD) and were considered significant at a probability (*P*) value of <0.05 . Intention to treat analysis with the last observation carried forward procedure was done.

Results

Participant disposition is presented in Fig. 1. Of the 54 participants who entered into the trial, 27 were assigned to saffron and 27 were assigned to donepezil. Three patients from the saffron group and four patients from the donepezil group dropped out. No significant differences were identified between patients randomly assigned to the group 1 or 2 condition with regard to basic demographic data including age, gender, level of education, and mean duration of illness (Table 1).

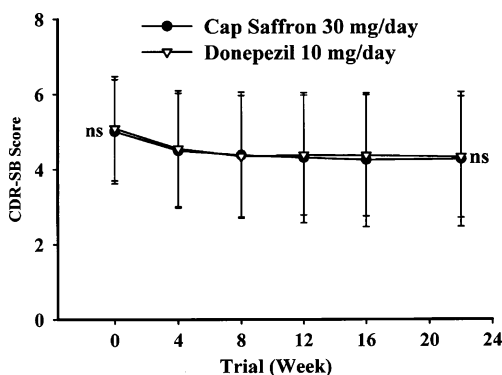


Fig. 3 Mean \pm SD scores of the two protocols on the CDR-SB score. *ns* nonsignificant

Table 2 Number of patients with adverse events

Adverse events	Saffron, <i>n</i> (%)	Donepezil, <i>n</i> (%)	<i>P</i>
Vomiting	1 (3.70)	7 (25.92)	0.05
Dizziness	2 (7.40)	5 (18.51)	0.42
Dry mouth	5 (18.51)	3 (11.11)	0.70
Fatigue	1 (3.70)	4 (14.81)	0.35
Hypomania	1 (3.70)	0	1.00
Nausea	2 (7.40)	6 (22.22)	0.25

Efficacy measures

ADAS-cog

The mean \pm SD scores of two groups of patients are shown in Fig. 2. There were no significant differences between the two groups at week 0 (baseline) on the ADAS-cog ($t=0.05$, $df=52$, $P=0.95$). The difference between the two treatments was not significant as indicated by the effect of group, the between-subjects factor (Greenhouse–Geisser corrected: $df=1$ and $F=0.004$, $P=0.95$). The behavior of the two treatment groups was similar across time (groups-by-time interaction, Greenhouse–Geisser corrected: $F=0.16$, $df=2.01$, $P=0.85$). The difference between the two treatments was not significant at the endpoint (week 22; $t=0.02$, $df=52$, $P=0.97$). The changes at the endpoint compared to baseline were -3.96 ± 3.50 (mean \pm SD) and -3.77 ± 3.80 for saffron and donepezil, respectively. No significant difference was observed on the change of scores of the ADAS-cog at week 22 compared to baseline in the two groups ($t=0.18$, $df=52$, $P=0.85$).

CDR-SB

The mean \pm SD scores of two groups of patients are shown in Fig. 3. There were no significant differences between the two groups at week 0 (baseline) on the CDR-SB ($t=0.19$, $df=52$, $P=0.84$). The difference between the two treatments was not significant as indicated by the effect of group, the between-subjects factor (Greenhouse–Geisser corrected: $df=1$ and $F=0.01$, $P=0.89$). The behavior of the two treatment groups was similar across time (groups-by-time interaction, Greenhouse–Geisser corrected: $F=0.20$, $df=1.58$, $P=0.76$). The difference between the two treatments was not significant at the endpoint (week 22; $t=0.01$, $df=52$, $P=0.89$). The changes at the endpoint compared to baseline were -0.77 ± 0.97 (mean \pm SD) and -0.83 ± 0.95 for saffron and donepezil, respectively. No significant difference was observed on the change of scores of the CDR-SB at week 22 compared to baseline in the two groups ($t=0.21$, $df=52$, $P=0.83$).

Clinical complications and adverse events

There was one death in the donepezil group due to myocardial infarction. Six adverse events were observed over the trial. The difference between the saffron and donepezil in the frequency of adverse events was not significant except for vomiting (Table 2). None of the adverse events was severe and did not cause dropout.

Discussion

Treatment strategies for AD will have to include a variety of interventions directed at multiple targets. So far, the outcomes with available approved medications for AD are often unsatisfactory, and there is a place for alternative medicine, in particular herbal medicine (Akhondzadeh and Abbasi 2006; Rafii and Aisen 2009). Herbal medicines are being used by about 80% of the world population primarily in the developing countries for primary health care. They have stood the test of time for their safety, efficacy, cultural acceptability, and lesser side effects (Akhondzadeh and Abbasi 2006).

The results of this clinical trial indicate that patients with mild-to-moderate AD receiving *C. sativus* extract experienced statistically significant benefits in cognition after 22 weeks treatment. The clinical relevance of these findings was emphasized by the improvements seen in both the ADAS-cog and CDR-SB measures in the saffron extract group. To our knowledge, this randomized, double-blind study is the first to be published on the effect of saffron extract as treatment for AD in comparison with an acetylcholinesterase inhibitors so it is not possible to draw any comparisons with others clinical studies. Nevertheless, there are increasing evidences to suggest the possible efficacy of saffron extract in the management of AD (Papandreou et al. 2006; Akhondzadeh et al. 2009). Indeed, in this double-blind and randomized comparison of extract of *C. sativus* and donepezil in the treatment of mild-to-moderate AD, extract of *C. sativus* at this dose was found to be effective similar to donepezil. The frequency of AEs was similar between saffron extract and donepezil groups with the exception of vomiting, which occurred significantly more frequently in the donepezil group. AEs were generally mild to moderate with no dropout as a result of adverse events in both groups. Moreover, behavioral symptoms are common in AD and represent a major source of the disease morbidity. Depression has been associated with more rapid cognitive decline increased caregiver burden, increases in patient care costs as a result of earlier institutionalization of the patient with AD, greater medication use and more adverse side effects, and more extensive institutional staffing needs (Starkstein et al. 2008). Interest-

ingly, several recent published clinical trials that have been shown antidepressant effect for saffron (Akhondzadeh et al. 2005; Akhondzadeh Basti et al. 2007). This study has several limitations including the small number of patients and a relatively short period of follow-up. In addition, further studies measuring biological markers are needed to elucidate the correlation between cognition improvement and pathophysiological alteration. Our results are in line with several basic studies that showed that saffron extract in oral application in mice improves the memory of mice per damaged with ethanol or crocin prevents the inhibitory effect of ethanol on long-term potentiation in mice. Low doses of saffron extract antagonized extinction of recognition memory in the object recognition test and scopolamine-induced performance deficits in the passive avoidance task (Sugiura et al. 1995a, b; Abe et al. 1998; Pitsikas et al. 2007). In addition, a recent study shows that saffron extract has antioxidant and anti-amyloidogenic activity and indicates the possible use of *C. sativus* stigma constituents for inhibition of aggregation and deposition of A β in the human brain (Papandreou et al. 2006). Finally, this study, for the first time, reinforces ethnopharmacological observations that saffron extract has a positive effect on cognitive function in AD (Schmidt et al. 2007).

In summary, this phase II study provides preliminary evidence of a possible therapeutic effect of saffron extract in AD. Moreover, saffron extract was generally safe and well tolerated in this small study up to 22 weeks of treatment.

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Ethics approval The protocol was approved by the Institutional Review Board (IRB) of Tehran University of Medical Sciences (Grant No. 8480).

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References

- Abdullaev FI, Espinosa-Aguirre JJ (2004) Biomedical properties of saffron and its potential use in cancer therapy and chemoprevention trials. *Cancer Detect Prev* 28:426–432
- Abe K, Saito H (2000) Effects of saffron extract and its constituent crocin on learning behaviour and long-term potentiation. *Phytother Res* 14:149–152
- Abe K, Sugiura M, Shoyama Y, Saito H (1998) Crocin antagonizes ethanol inhibition of NMDA receptor-mediated responses in rat hippocampal neurons. *Brain Res* 787:132–138
- Akhondzadeh S (1999) Hippocampal synaptic plasticity and cognition. *J Clin Pharm Ther* 24:241–248
- Akhondzadeh S (2007) Herbal medicine in the treatment of psychiatric and neurological Disorders. In: L'Abate L (ed) *Low-cost approaches to promote physical and mental health: theory research and practice*. Springer, New York, pp 119–138
- Akhondzadeh Basti A, Moshiri E, Noorbala AA, Jamshidi AH, Abbasi SH, Akhondzadeh S (2007) Comparison of petal of *Crocus sativus* L. and fluoxetine in the treatment of depressed outpatients: a pilot double-blind randomized trial. *Prog Neuropharmacol Biol Psychiatry* 31:439–442
- Akhondzadeh S, Abbasi SH (2006) Herbal medicine in the treatment of Alzheimer's disease. *Am J Alzheimers Dis Other Demen* 21:113–118
- Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M (2003a) *Salvia officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomized and placebo-controlled trial. *J Clin Pharm Ther* 28:53–59
- Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M (2003b) *Melissa officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomised, placebo controlled trial. *J Neurol Neurosurg Psychiatry* 74:863–866
- Akhondzadeh S, Tahmacebi-Pour N, Noorbala AA, Amini H, Fallah-Pour H, Jamshidi AH, Khani M (2005) *Crocus sativus* L. in the treatment of mild to moderate depression: a double-blind, randomized and placebo-controlled trial. *Phytother Res* 19:148–151
- Akhondzadeh S, Shafiee Sabet M, Harirchian MH, Togha M, Cheraghmakani H, Razeghi S, Hejazi SS, Yousefi MH, Alimardani R, Jamshidi AH, Zare F, Moradi A (2009) Saffron in the treatment of patients with mild to moderate Alzheimer's disease: a 16-week, randomized and placebo controlled trial. *J Clin Pharm Ther* (in press)
- Becker RE, Greig NH (2008) Alzheimer's disease drug development in 2008 and beyond: problems and opportunities. *Curr Alzheimer Res* 5:346–357
- Birks J, Grimley A, Evans J (2009) *Ginkgo biloba* for cognitive impairment and dementia. *Cochrane Database Syst Rev* 21: CD003120
- Citron M (2004) Strategies for disease modification in Alzheimer's disease. *Nat Rev Neurosci* 5:677–685
- Ernst E (2006) Herbal medicines—they are popular, but are they also safe? *Eur J Clin Pharmacol* 62:1–2
- Folstein MF, Folstein SE, McHugh PR (1975) Mini-mental state. A practical method or grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12:189–198
- Golde TE (2005) The A β hypothesis: leading us to rationally-designed therapeutic strategies for the treatment or prevention of Alzheimer disease. *Brain Pathol* 15:84–87
- Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL (1982) A new clinical scale for the staging of dementia. *Br J Psychiatry* 140:566–572
- Izzo AA, Capasso F (2006) Herbal medicines to treat Alzheimer's disease. *Trends Pharmacol Sci* 28:47–48
- Mantle D, Pickering AT, Perry E (2002) Medical plant extracts for treatment of dementia. A review of their pharmacology, efficacy and tolerability. *CNS Drugs* 13:201–213
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 34:939–944
- Papandreou MA, Kanakis CD, Polissiou MG, Efthimiopoulos S, Cordopatis P, Margarity M, Lamari FN (2006) Inhibitory activity on amyloid-beta aggregation and antioxidant properties of *Crocus sativus* stigmas extract and its crocin constituents. *J Agric Food Chem* 15:8762–8768
- Pitsikas N, Zisopoulou S, Tarantilis PA, Kanakis CD, Polissiou MG, Sakellaridis N (2007) Effects of the active constituents of *Crocus sativus* L. crocins on recognition and spatial rats' memory. *Behav Brain Res* 183:141–146
- Raffi MS, Aisen PS (2009) Recent developments in Alzheimer's disease therapeutics. *BMC Med* 19:7
- Rosen WG, Mohs RC, Davis KL (1984) A new rating scale for Alzheimer's disease. *Am J Psychiatry* 141:1356–1364
- Schmidt M, Betti G, Hensel A (2007) Saffron in phytotherapy: pharmacology and clinical uses. *Wien Med Wochenschr* 157:315–319
- Starkstein SE, Mizrahi R, Power BD (2008) Depression in Alzheimer's disease: phenomenology, clinical correlates and treatment. *Int Rev Psychiatry* 20:382–388
- Sugiura M, Shoyama Y, Saito H, Nishiyama N (1995a) Crocin improves the ethanol-induced impairment of learning behaviors of mice in passive avoidance tasks. *Proc Japan Acad Ser B* 1:319–324
- Sugiura M, Shoyama Y, Saito H, Abe K (1995b) Ethanol extract of *Crocus sativus* L. antagonizes the inhibitory action of ethanol on hippocampal long-term potentiation in vivo. *Phytother Res* 9:100–104
- Tedeschi G, Cirillo M, Tessitore A, Cirillo S (2008) Alzheimer's disease and other dementing conditions. *Neurol Sci* 29 (Suppl):301–307
- Tsuno N (2009) Donepezil in the treatment of patients with Alzheimer's disease. *Expert Rev Neurother* 9:591–598
- Wake G, Court J, Pickering A, Lewis R, Wilkins R, Perry E (2000) CNS acetylcholine receptor activity in European medicinal plants traditionally used to improve failing memory. *J Ethnopharmacol* 69:105–114