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Effectiveness of saffron in the treatment of mild to moderate Alzheimer's disease with ADAS-cog score

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***Abstract*---Introduction**: large levels of glucocorticoids and stress results structural and functional changes in brain and hippocampus, limbic system has a key role in cognitive functions including learning and memory. Alzheimer's disease (AD) is a chronic neurodegenerative disease. **Objective**: the AIM of this study was to assess the efficacy of saffron in the treatment of mild to moderate Alzheimer's disease (AD). **Methods:** fifty-six patients of 55 years old were eligible to participate in this study. the study is a double-blind study of parallel groups of patients with AD. **Results**: saffron is effective similar to donepezil in the treatment of mild to moderate AD after 22 weeks. The safety of saffron is comparatively similar like donepezil. The side effects presented with saffron and donepezil groups likely same. The major parameter taken was Alzheimer's disease assessment Scale-cognitive subscale score evaluated with baseline. The safety of saffron was also recorded systemically. Participators were given a capsule saffron 30 mg/day (15 mg twice daily) or donepezil 10 mg/day (5 mg twice per day). **Conclusion**: this study provides mainly suggests that possible therapeutic effect of saffron extract at least in short-term treatment of patients with mild-to0moderate Alzheimer's disease.

***Keywords*---**clinical trial, cholinesterase inhibitor, saffron, dementia.

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 giant 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 age of 65 and 75 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; Tedeschiet al.2008) deposition of amyloid-β (Aβ) in the brain is a neuronal damage (golde 2005). Although a magic bullet for AD has clear 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 diseases, retard its progression once it has set in, or offer some symptomatic relief (becker and greig 2008; rafi 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 system. Counteracting overproduction of amyloid-β (Aβ) 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 world population, mainly in the developing countries, for primary health care because of better culture 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 (mantel 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 Aβ processing, protection against apoptosis and oxidative stress, and anti-inflammatory effects (wake et al. 2000; akhondzadhe and abbasai 2006).

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 stigma (the top of the centre part of a flower that receives the pollen which allows it to from new seeds) of crocus sativus L.) is

determined by the existence of three main secondary metabolite; crocin and its derivatives which are responsible for colour; picrocrocin which is responsible for taste; and safranal which is responsible for odour (Schmidt et al. 2007). This plant belongs to the iridaceace 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 relives renal colic, reduces stomach ache, and relieves tension (akhondzadhe and abbasai 2006; Schmidt et al. 2007). It has been shown that administration of extract of C.sativus L. antagonized ethanol induced memory impairment in the passive avoidance task in the mouse, and the constituent of saffron extract, crocin, prevented ethanol-induced inhibition of hippocampal long-term potentiation , a form of activity-depended synaptic plasticity that may underlie learning and memory(sugiura et al. 1995a, b; akhondzadhe 1999). In additional, it has also been reported that crocin counteracted ethanol inhibition of N-methyl-D-aspertate receptor-mediated responses in rat hippocampal neurons (abe et al. 1998). Low doses of C.sativus extract antagonised extinction of recognition memory in the object recognition test and scopolamine-induced performance deficits in the passive avoidance task in rat (pitsikaset al.2007).

Materials and Methods

The study design: The proposal of this study, 22-week, double-blind study of patients with mild-to-moderate Alzheimers disease and was conducted in hospital of Indore, from October 2022 to November 2023.
Measurements: The psychometric measure, which includes the MMSE, Alzheimer's disease assessment scale- cognitive subscale (ADAS-cog) is performed to monitor the global cognitive and clinical profile of the subjects.
Interventions: Patients were randomized to receive capsule of saffron or capsule of donepezil in a 1:1 ratio using a computer-generated code. Donepezil and saffron capsules are visually identical in terms of shape and colour. In this double-blind study, patients are randomly assigned to receive capsule saffron 30 mg/kg (15 mg twice per day) or capsule donepezil 10 mg/kg (5mg twice per day) for 22-weeks study.

Following the screening phase, a capsule of saffron 15 mg or capsule of donepezil 5mg is given for first 4 weeks, after which the dose is increased to two capsules of saffron or donepezil per day for the rest of the study.

Preparation of capsule of saffron
The saffron used in this study is donated by Sri LalithaMahaa Tripura Sundari Devi Nursery (Tirupati, Andhra Pradesh). The saffron capsules used in this study will prepared as follows: 120 g of dried and milled C. sativus L. stigma will extracted with 1800 mL ethanol (80%) by percolation procedure in three steps, and then the ethanol extract will be 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 (disintegrate). 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 were 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 were report or observed, had record at each visit. Routine physical examination was conducted at each clinical visit. Complete physical examinations, including 12 lead electrocardiogram recordings, was conducted at weeks 0,8, and 22.

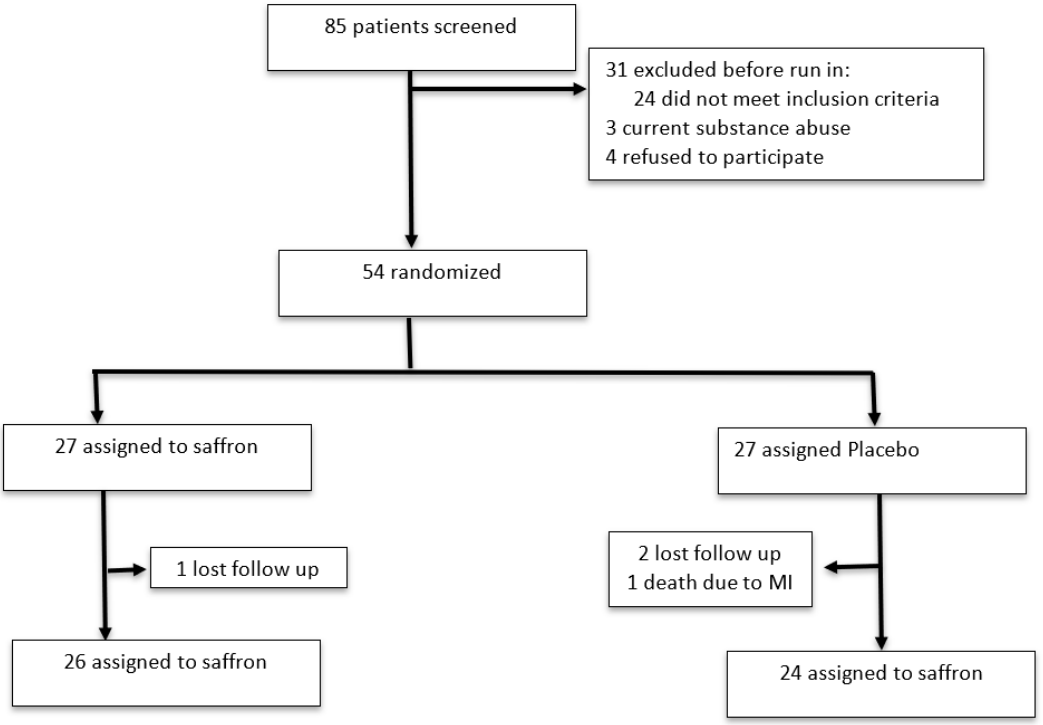
Sample size calculations:
On the basis of previous literature prevalence statistics on mean ADAS –cog with a standard deviation of 3, a power of 90%, a two-sided significance level of 0.05, and an attrition rate of 25%. Therefore, a sample size of 150 will be calculated for each group. IBM SPSS Statistic 20 (IBM Corporation, Armonk, NY, USA) will be used for data analysis. All analyses will be 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 as the between-subject factor and the study measurements as the within-subject variables (time). Independent t test will be used to analyse the 2 groups based on ADAS-cog score. The frequency of side effects and the number of patients who remained stable throughout this study will be compared between two trial groups using chi-square test. t. A p-value of < 0.05 was considered statistically significant.

Results

From January 2020 to March 2023, 85 patient were screened for the trail, of whom 52 were randomized to either saffron or control capsules. Figure 1 shows the trail profile. There was no variations in baseline property including, age, gender, time of illness and education level (table1).

Efficacy measures
ADAS-cog
The mean ± SD score of two groups of patients are shown in fig 1. There were no significant differences between the saffron and control groups at the initial week on the ADAS-cog
(t=0.04, df= 50, P= 0.94). the difference between two groups was not significant as used by the effect of group. The character of the two treatment groups was same throughout the treatment. At the end point of the treatment not significant between the two groups.there was no significant difference was observed on the change of score of the ADAS-cog at week 22 compared to baseline in the two group (t=0.16, df=50, P=0.84).

Study Design:



Discussion

Alzheimers disease, a major public health problem, treatment strategies for AD will have to include a variety of methods needed at multiple target.as of, the results with current treatment for AD are not satisfactory and there is a alternative medicine in herbal medicine (Akhondzadeh and Abbasi 2006;Rafi and Aisen 2009). Herbal medicine is being used by about 75% of the world population in the developing countries for health care. The evaluated the test of time for their safety, efficacy, cultural acceptability and minimal side effects (Akhondzadeh and Abbasi 2006).

The current study indicates that the saffron capsules are useful for the treatment of patients with mild to moderate AD as proved by improvement in the ADAS-cog scale. Relatively so many studies are emerging on the same topic to prove that saffron has efficacy in the treatment of AD. However, there are increased evidences to suggest the possible efficacy of saffron capsules in the management of AD (Papandreou et al.2006:Akhondzadeh et al.2009)

These studies proved that oral saffron improved the dementia of mice predamaged with ethanol and saffron prevents the inhibitory effects of ethinal on LTP in mice.(Sugiura et al.1995, Papandreou et al.2006, pitiskas N et al 2006, pitiskas N and Zissopoulos S et al 2007). Minimal doses of saffron inhibits the extinction of recognition memory in the object recognition test and reverse the scopolamine – induced performance in the passive avoidance task (Sugiura et al.1995)

The results of this tral are consistent with the resul of those basic studies (Sugiuraet al.1995, Papandreou et al.2006, pitiskas N et al 2006, pitiskas N and Zissopoulos S et al 2007) as well as the reported antioxidant and antiamyloidogenic activity of an saffron stigmas. (Papandreous MA et al 2006).

The limitations of present study include the small number of patients and a relatively short period of follow-up. Therefore, further controlled studies should be undertaken. The use of herbal medicines in the treatment of AD should be compared with the pharmacological treatment currently in use.

Conclusion

This study indicates that at least in the short-term saffron capsule is safe and effective in mild –moderate AD. More randomized controlled studies are required further verify this herbal remedy.

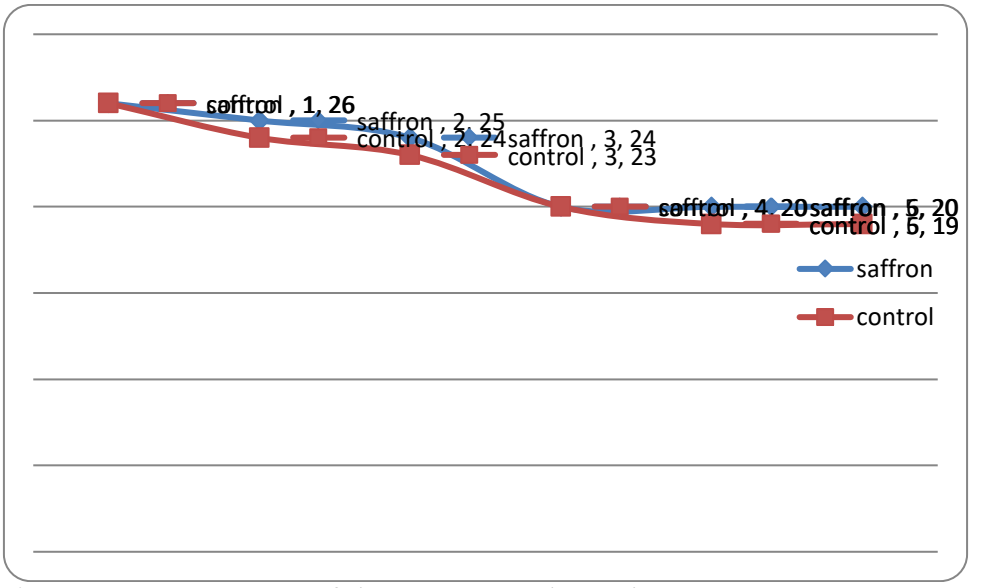


Fig 1 mean ± SD scores of the two protocols on the ADAS-Cog score, ns no significant

Table-1

	Saffron group	Control group	p
Gender	Male: 15, female:12	Male: 15, female:12	ns
Age (mean ± SD)	73.55± 4.98(year)	74.15± 5.08(year)	ns
Level of education	Under diploma: 15 Diploma:7 Higher diploma:5	Under diploma: 17 Diploma:6 Higher diploma:4	ns
Time since diagnosis (mean ± SD)	19.65±9.19(month)	18.05±4.10(month)	

References

1. 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
2. Abe K, Saito H (2000) Effects of saffron extract and its constituent crocin on learning behaviour and long-term potentiation. Phyt-other Res 14:149–152
3. 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
4. Akhondzadeh S (1999) Hippocampal synaptic plasticity and cognition. J Clin Pharm Ther 24:241–248
5. 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
6. AkhondzadehBasti 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. ProgNeuropsychopharmacolBiol Psychiatry 31:439–442
7. Akhondzadeh S, Abbasi SH (2006) Herbal medicine in the treatment of Alzheimer's disease. Am J Alzheimers Dis Other Demen21:113–118
8. Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, JamshidiAH, Khani M (2003a) Salvia officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a doubleblind, randomized and placebo-controlled trial. J Clin Pharm Ther 28:53–59
9. Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, JamshidiAH, 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 NeurolNeurosurgPsychiatry 74:863–866.
10. Akhondzadeh S, Tahmacebi-Pour N, Noorbala AA, Amini H, Fallah-PourH, 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.
11. Akhondzadeh S, ShafieeSabet M, Harirchian MH, Togha M, Cheraghmakani H, Razeghi S, Hejazi SS, Yousefi MH, AlimardaniR, 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.
12. Birks J, Grimley A, Evans J (2009) Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev 21: CD003120.
13. 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 ClinPharmacol 62:1–2.
14. 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.

15. Golde TE (2005) The Aβ hypothesis: leading us to rationally designed therapeutic strategies for the treatment or prevention of Alzheimer disease. Brain Pathol 15:84–87
16. 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
17. Izzo AA, Capasso F (2006) Herbal medicines to treat Alzheimer's disease. Trends PharmacolSci 28:47–48
18. 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
19. McKhann G, Drachman D, Folstein M, Katzman R, Price D, StadlanEM (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
20. 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
21. 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. BehavBrain Res 183:141–146
22. Rafii 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
23. Schmidt M, Betti G, Hensel A (2007) Saffron in phytotherapy: pharmacology and clinical uses. Wien Med Wochenschr157:315–319
24. Starkstein SE, Mizrahi R, Power BD (2008) Depression in Alzheimer's disease: phenomenology, clinical correlates and treatment. Int Rev Psychiatry 20:382–388
25. Sugiura M, Shoyama Y, Saito H, Nishiyama N (1995a) Crocinimproves the ethanol-induced impairment of learning behaviors of mice in passive avoidance tasks. Proc Japan AcadSer B 1:319–324
26. 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
27. Tedeschi G, Cirillo M, TessitoreA, Cirillo S (2008) Alzheimer's disease and other dementing conditions. NeurolSci 29 (Suppl):301–307
28. Tsuno N (2009) Donepezil in the treatment of patients with Alzheimer's disease. Expert Rev Neurother 9:591–598
29. 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 Ethnopharmacol69:105–114