

Effect of combination of honey, saffron (*Crocus sativus* L.) and sedge (*Cyperus rotundus* L.) on cognitive dysfunction in patients with Alzheimer's disease

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ABSTRACT

Background and aims: Alzheimer's disease is a progressive disorder of nervous system that leads to dementia in patients. This study was conducted to determine the effect of combination of honey, saffron (*Crocus sativus* L.) and sedge (*Cyperus rotundus* L.) on cognitive dysfunction in patients with Alzheimer's disease.

Methods: This double-blinded clinical trial study enrolling a sample size of 30 subjects was conducted per cross-over method. The patients with mild Alzheimer's disease obtaining the scores 12 in cog-ADAS scale were enrolled into the study. The participants were randomly assigned into two groups of A and B. During the first 2 months in group A, placebo was given, and group B underwent treatment with the combination under study. After a one-month period of washout, the same procedure was run reversely in two groups. Finally, the data analysis was done by SPSS software using descriptive and analytical tests.

Result: Mann-Whitney test indicated no difference in mean cognitive dysfunction between two groups in neither of periods ($P > 0.05$). Also, Friedman test showed no change in cognitive dysfunction during the study in neither of groups (group A: $P = 0.287$, group B: $P = 0.158$).

Conclusion: Simultaneous use of honey, *C. rotundus* and *C. sativus* has no more pronounced effect than placebo on cognitive dysfunction in patients with mild to moderate Alzheimer's disease. It is recommended that future studies of this compound be done on patients of younger age and its preventive effects be addressed.

Keywords: Alzheimer's disease, *Cyperus rotundus*, *Crocus sativus*, Honey.

INTRODUCTION

Alzheimer's disease is a progressive and degenerative disease of the central nervous system that causes deterioration of intellectual capacity. The exact origin of this disease is unknown, but several changes such as brain shrinkage, loss of brain cells, development of plaques of aging consisting of beta-amyloid peptide and neurofibrillary tangles in brain cells

are the most important symptoms of the disease.^{1,2} Alzheimer's disease is the most common cause of dementia which is characterized by a progressive decline in cognition, leading to dysfunction of memory and abstract thinking and social or occupational disability in the patients.² This disease makes the patients disable and fully dependent, and indirectly causes

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economic and psychological problems for the rest of family members and community.³ Alzheimer's disease is an important cause of morbidity and mortality worldwide, so that it is the fifth leading cause of death in the population over 65 years in the USA.⁴ On the other hand, the incidence rate is similar worldwide, with a mean prevalence of 3 new cases per 100000 individuals under 60 years and 125 cases per 100000 individuals above 60 years.⁵ Alternative (non-chemical) therapy is one of the therapies considered for Alzheimer's disease. For this, a variety of approaches such as herbal remedies, aromatherapy, massage therapy, music therapy, acupuncture, dietary supplements, melatonin and severe light may be used.^{6,7} Alternative therapies, especially medicinal plants, have opened a new way to treat Alzheimer's disease. Researches indicate that honey can play a critical role in enhancing memory and can be used as an agent of preventing dementia.^{8, 9} Saffron (*Crocus sativus* L.) is one of the medicinal herbs with established desired effects on memory strengthening in laboratory animals. Besides, it has exerted desired effects on learning and concentration increase in laboratory animals.^{10, 11} A study on the effect of oral and parenteral use of *C. rotundus* on learning and memory in male rats, demonstrated that the use of this plant promoted retrieval of memory, with a more pronounced effect on rats' long term memory.¹² In some empirical books, use of *C. rotundus*, *C. sativus*, honey and currant has been recommended to resolve forgetfulness and distraction.¹³ Traditional medicine and alternative medicine have recently become particularly significant. On the other hand, the people of Chaharmahal and Bakhtiari province use the combination of *C. rotundus*, honey and *C. sativus* as memory-reinforcing. Since no study of this

combination has been yet conducted on humans, the recovery of cognitive dysfunction is significant for Alzheimer's disease patients and in light of no similar study done to date. The present study aimed to determine the effect of combination of honey, *C. sativus* and *C. rotundus* on cognitive dysfunction in patients with mild to moderate Alzheimer's disease.

METHODS

This study was conducted as a double-blinded (lack of awareness of the groups under study by the researcher and statistician) clinical trial study in cross-over method. Sampling was in convenience method. This means that after obtaining the written consent and explaining the objectives of the study, all patients were enrolled with mild to moderate Alzheimer's disease referring neurology clinic of Kashani Hospital who were eligible for the study, after determining the cognitive status measured by the standard scale Assessment Scale-Cognitive Behavior= ADAS-cog.¹⁴ The patients with mild Alzheimer's disease obtaining the scores 12 in cog-ADAS scale were considered as eligible for the study.¹⁴ Sensitivity to *C. rotundus*, honey and *C. sativus*, history of diabetes and suffering from other dementia-causing diseases were considered as exclusion criteria. Two groups were matched for age and sex, and eventually 30 patients with mild to moderate Alzheimer's disease, were randomly divided into two groups of 15 individuals in each group, A and B. In the first step, group B, in addition to the routine treatment of Alzheimer's disease, received daily two capsules, each containing 30 mg *C. sativus*¹⁵ and 500 mg *C. rotundus*,¹⁶ one morning and one evening for two months. In each step, one

teaspoonful of oral honey (5 g) was prescribed for the patients. Then, at the end of this two-month period, cognitive status of the patients was measured in both groups by the ADAS-cog scale. After the first step during a one-month period of washout, treatment with the combination of honey, *C. sativus* and *C. rotundus* was discontinued in two groups and then the second step of the study began. In the second step, firstly cognitive status of all patients was measured by ADAS-cog. Then, group A underwent treatment with honey, *C. sativus* and *C. rotundus* combination in addition to Alzheimer's disease routine treatment for two months, as with group B in the first step. Group B was given placebo in addition to the routine treatment for two months, as with group A in the first step. At the end of the second step, the cognitive status of all patients was also measured by ADAS-cog. The collected data were entered into SPSS software, mean age and gender distribution of two groups were investigated by t- test and chi square, respectively. Mann-Whitney and Friedman tests were used for data analysis, as well.

RESULTS

Overall, 30 patients with mild to moderate Alzheimer's disease were assigned into two groups of A and B. In group A, firstly placebo was given to the patients for two months. Then, after a one-month period of washout, the patients were given the combination of *C. rotundus*, *C. sativus* and honey for two months. In group B, firstly the combination treatment used in this study was given to the patients for two months, and after a one-month period of washout, placebo was given to the patients for two months. The patients' mean age in group A was 69.12 ± 11 (range; 57-88) years and in group B was 64.7 ± 12.7 (range; 50-83)

years, with no significant difference between two groups by t-test ($P=0.311$). Overall, 17 (56.7%) patients were female and 13 (43.3%) were male. This ratio was similar in two groups using chi-square ($P=0.731$). The cognitive dysfunction mean by ADAS-cog during study periods is summarized in Table 1. Mann-Whitney test showed no difference in cognitive dysfunction between two groups (Table 1).

Table 1: Cognitive dysfunction mean by ADAS-cog in two groups of A and B in study steps

Study steps	Mean \pm Standard deviation		P-Value
	Group A	Group B	
Baseline	2.9 \pm 8.3	1.8 \pm 8	0.98
After two months	2.8 \pm 8.8	2.1 \pm 7.8	0.36
After washout	2.6 \pm 8.6	1.9 \pm 8.2	0.083
After the second two months	2.8 \pm 8.4	2.6 \pm 7.9	0.083

Also, Friedman test showed no change in cognitive dysfunction during the study in neither of the groups (group A: $P=0.287$, group B: $P=0.158$).

DISCUSSION

In this study conducted to determine the effect of honey, *C. sativus* and *C. rotundus* combination on cognitive dysfunction in patients with Alzheimer's disease, statistical analysis of the data indicated no significant difference in mean cognitive dysfunction between two groups in all steps of the study. In other words, there was no significant difference in mean cognitive dysfunction between taking the therapeutic combination (honey, *C. sativus* and *C. rotundus*) and taking placebo in either of A or B groups. No similar study has been found on the effect of simultaneous use of honey, *C. sativus* and

C. rotundus on cognitive dysfunction or memory in humans. In Al-Rahbi et al. study, therapeutic honey (Tualang honey) was demonstrated to possibly reinforce short-term and long term memory in rats.¹⁷ Another study found that honey as a natural substance can exert preventive effect on dementia in the Middle East populations.⁹ In these studies, the type and/or dose of honey applied to reinforce the memory could influence the findings.

However, the studies of *C. sativus* found the findings inconsistent with the present study findings. For example, a systematic review of pharmacologic effects of *C. sativus* indicated that *C. sativus*, besides positive effects on other parts of the body, could exert desired effects on central nervous system, as well. These effects were including reinforcing memory and learning, and protecting neurons.¹⁸ In Papandreou et al. study, *C. sativus* played an effective role in promoting memory and learning in mice.¹⁹ In another study by Akhondzadeh et al. on saffron effects on the symptoms of mild to moderate Alzheimer's disease, cognitive activities improved in the patients. However, Akhondzadeh et al. pointed out that the effects of herbal medicine can represent different responses in the treatment of behavioral and psychological symptoms of dementia,¹⁴ which could explain the inconsistency of the findings between other studies and the present study, not to mention the difference in treatment duration and prescribed *C. sativus* dose. Researches indicate that sedge is known as a herbal medicine used for treatment of Alzheimer's disease in Iran.²⁰ In a study of the effect of sedge hydroalcoholic extract on learning and memory in rats with Alzheimer's disease, sedge was shown to have regenerating effects on memory and behavioral disorders.²¹ Dhivya et al. in a study of effective medicinal plants on the treatment of Alzheimer's disease, considered sedge as a herbal medicine contributing in inhibiting

cholinesterase, which could be helpful in treating Alzheimer's disease.²² In 2011, Sharma and Gupta obtained similar findings on cholinesterase-inhibiting effects of sedge in animal models.²³ Regarding the above studies, further researches should be carried out to study the effects of *C. sativus* in humans. However, prior to the present study, no study has been conducted to study the impact of *C. rotundus* on human memory and cognitive dysfunction.

CONCLUSION

Based on the findings of the present study, simultaneous use of honey, *C. rotundus* and *C. sativus* has no more pronounced effect than placebo on cognitive dysfunction in patients with mild to moderate Alzheimer's disease. Regarding the memory-reinforcing properties for these three foods demonstrated by recent studies and cited in traditional and religious books, study of individuals of younger age who are likely to develop memory dysfunction and Alzheimer's disease in the elderly could yield better results. Also, this combination which has preventive role rather than therapeutic effects is recommended to be investigated in future studies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

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