

# Effects of herbal medicine on memory impairment in electroconvulsive therapy

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**BACKGROUND:** The usefulness of electroconvulsive therapy (ECT) in the management of mood disorders would be improved if its related cognitive impairment is attenuated properly. In this study we investigated the effects of using a combination of *Crocus sativus* (CS), *Cyperus rotundus* (CR), and honey in the treatment of ECT-induced memory impairment. **METHODS:** In this randomized double-blind clinical trial, patients with mood disorders who were candidates for ECT were selected by random sampling method. They were then randomized into 2 groups of intervention and placebo. The two groups received 9 grams of an herbal combination of CS, CR, and honey or identical placebo twice daily for 40 days from the ECT initiation time. ECT was performed 3 times a week. Cognitive status was examined using Addenbrooke's Cognitive Examination-Revised (ACE-R) test. Patients were examined on 5 occasions, i.e. before ECT, after the fourth and the last session, and one and two months after the last session. **RESULTS:** Mean scores of ACE-R were compared between the two studied groups and between the studied occasions using repeated measures analysis of covariance (ANCOVA). Overall, 84 patients were randomized into two groups of intervention and placebo. Mean scores of ACE-R were not different between the two studied groups in the studied occasions ( $p > 0.05$ ). However, ACE-R scores increased significantly in the intervention group after one or two months after the last ECT session ( $p < 0.05$ ). Time and interaction effects were significant but the intervention effect was not. **CONCLUSIONS:** Our findings confirmed the memory improving effects of CR, CS, and honey. However, achieving more conclusive results requires larger sample size and longer duration of study.

**KEYWORDS:** Electroconvulsive Therapy, Memory Impairment, Honey, *Crocus Sativus*, *Cyperus Rotundus*

## BACKGROUND

Electroconvulsive therapy (ECT) is considered as a safe and the most effective procedure with no absolute contraindications in the treatment of major depressive disorder, bipolar disorder, and many severe mental illnesses. Its superiority in this regard was developed due to the technique improvement over 70 years.<sup>[1,2]</sup>

Despite the increasing trend of using ECT in the past decades, some complications have limited its application as a treatment option. The most important adverse effect of ECT, which made its use a controversial issue, is its related long-term cognitive changes especially in the memory system (represented as anterograde or retrograde memory impairment).<sup>[3,4]</sup> Anterograde amnesia is mild and temporary whereas the retrograde form may be severe and last for 3-6 months after ECT.<sup>[4]</sup>

The memory impairment among patients after ECT has been well characterized and reported in several studies. Although the exact related mechanisms are not understood yet, some processes

have been suggested.<sup>[5]</sup> Recent evidence has also confirmed the importance of the mentioned complications based on patient perceptions. According to these researches, 29-55% of patients experienced long lasting memory loss after treatment.<sup>[6]</sup>

Many pharmacological approaches have been performed to reduce or attenuate the amnesia caused by ECT through finding its underlying mechanisms.<sup>[7,8]</sup> However, it seems that it does not work properly due to unknown factors. On the other hand, in accordance with pharmacological researches, recent studies have explored the efficacy of herbal medicine for ECT-induced memory deficits.<sup>[9,10]</sup>

Herbal medicine is considered as a popular form of healthcare worldwide. In fact 75-80% of the world population, especially in developing countries, use this kind of medicine because of its better cultural acceptability, appropriate compatibility with human body, and lesser adverse effects.<sup>[11]</sup> The applications of herbal and complementary medicine have also increased in developed countries in the last few

years.<sup>[11]</sup> In spite of similarities in using different herbal and complementary medicines for specific conditions among different countries and ethnic groups, some remedies belong to particular areas.

In Iran, the effects of this kind of medicine for improving memory deficits have been mentioned in traditional and Islamic books. The efficacy of *Crocus sativus* (saffron), *Cyperus rotundus*, and honey have been reported in this field.<sup>[12]</sup>

*Crocus sativus* (CS), commonly known as saffron, has been used for various medicinal purposes. It is cultivated in different parts of the world including Iran.<sup>[13]</sup> Experimental evidence has proposed the effectiveness of CS in learning and memory processes due to its active components such as water-soluble carotenoids (crocins), glucosides (safranal and picrocrocin), flavonoids (quercetin and kaempferol) and monoterpene aldehydes. Among these components, crocins have an important role in cognitive and memory impairment.<sup>[14]</sup>

Due to the antibacterial, antioxidant, cytotoxic, and apoptotic activities of its tubers extracts, *Cyperus rotundus* (Cyperaceae) (CR) has long been used as food for health care promotion and also as a drug for medicinal purposes in the management of certain diseases.<sup>[15]</sup> The central nervous system (CNS) activities of the roots and rhizomes extracts of CR have been reported.<sup>[16]</sup>

Honey is considered as part of traditional medicine with great healing properties worldwide. Several studies have been compiled on its nutritional and health aspects. Honey possesses different nutritional and biological effects including antioxidant, immunoregulatory, and antimicrobial effects.<sup>[17]</sup> The antioxidant effect of honey, mainly because of its phenolic compounds, is known as the link between its consumption and improvement of memory deficits.<sup>[18]</sup>

Therefore, it is a fact that the usefulness of ECT would be improved if its related cognitive impairments are attenuated properly. We hence investigated the effects of a combination of the 3 mentioned herbal medicines in the treatment of ECT-induced memory impairment.

## METHODS

In this randomized double-blind clinical trial, patients over 18 years of age who were diagnosed with mood disorders and were candidates for ECT

were enrolled. Subjects were selected by random sampling method in 2011.

The Medical Ethics Committee of the Isfahan University of Medical Sciences (Isfahan, Iran) approved the study protocol and all subjects gave their written consents.

Inclusion criteria were the diagnosis of mood disorders by a psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV) criteria<sup>[19]</sup> and having the experience of 6-10 ECT sessions. Subjects were only included if they were able to take oral medicine.

Patients suffering from intellectual disability, dementia, psychosis, delirium, amnesia, and diabetes mellitus, and those taking other herbal medicines at the time of the study, as well as pregnant women were excluded.

Selected patients were randomized into two groups of intervention and placebo. Patients received 9 grams of the herbal combination of CS, CR, and honey or identical placebo, both administered twice daily for 40 days from the ECT initiation time. Both the placebo and herbal combination capsules were supplied by a pharmacological institute in Shahrekord, Iran.

The herbal combination capsules contained 500 mg CR, 30 mg CS, and 5 g honey. The placebo capsules contained starch with 5 g melted sugar.

Baseline characteristics of patients were recorded using a questionnaire. ECT was performed bilaterally in temporal lobe 3 times a week. Cognitive status of the studied population in the two groups was examined using Addenbrooke's Cognitive Examination-Revised (ACE-R) test for Persian-speaking population.<sup>[20]</sup> Patients were examined on 5 occasions, i.e. before ECT, after the fourth session of ECT, following the last session of ECT, and one and two months after the last ECT session. The mean scores of ACE-R were compared in the studied occasions between the two groups and between the studied occasions.

## ECT

ECT was performed bilaterally in temporal lobe using an electroconvulsive device. Seizure threshold, defined as the stimulus dosage that elicited a seizure of at least 25 s according to the cuff method, was determined during the first session with empirical stimulus titration. If the starting stimulus dose failed to elicit a seizure of at least 25 s, stimulus charge was increased according to the titration schedule and the patient was restimulated after 30 s. For the second treatment, the

stimulus dosage was set at previous effective threshold.

### ACE-R test

The ACE-R is a brief cognitive test that assesses five cognitive domains, namely attention/orientation, memory, verbal fluency, language, and visuospatial abilities. The total score of the scale is 100 and higher scores indicate better cognitive functioning.<sup>[21]</sup> In this study, we used the validated form of ACE-R test for Persian-speaking population (assessed by Pouretamad et al.). The sensitivity and specificity of the Persian ACE in discriminating mild cognitive impairment from a normal population at a cut-off point of 84 have been determined as 93% and 91%, respectively.<sup>[20]</sup>

### Statistical analysis

Statistical analyses were performed by repeated measures analysis of covariance (ANCOVA) in SPSS<sub>17</sub> (SPSS Inc., Chicago, IL, USA.). P-values less than 0.05 were considered to be statistically significant.

## RESULTS

In this study, 84 patients with mood disorders were randomized into two groups of intervention and placebo. The relative frequency of bipolar mood disorder, manic-depressive disorder, and other mood

disorders among the studied population was 30.3%, 28.8%, and 40.9%, respectively. The mean age and education period of the participants was  $41.2 \pm 12.6$  and  $9.1 \pm 4.7$  years, respectively. From the studied population, 51.4% were male and 48.6% were female. Moreover, 78.1% of the subjects were married. The mean baseline ACE-R score was  $72.2 \pm 14.5$ .

During the study, 6 patients in the intervention group and 4 in the placebo group were missed. The characteristics of the participants in the intervention and placebo groups are presented in table 1. On the other hand, table 2 compares ACE-R scores before the fourth session, after the last session, and 1 and 2 months after the termination of ECT using repeated measures ANCOVA. Mean ACE-R scores in the two groups during the course of study are demonstrated in figure 1.

The results indicated that using this combination therapy could have proper effects on memory impairment, especially one or two months after the last ECT session. However, it did not have significant effects during or immediately after that the ECT period. The significant P-values of time effect and interaction effect indicated that this combined herbal treatment was effective for memory improvement during time (minimum 1-2 months after treatment initiation).

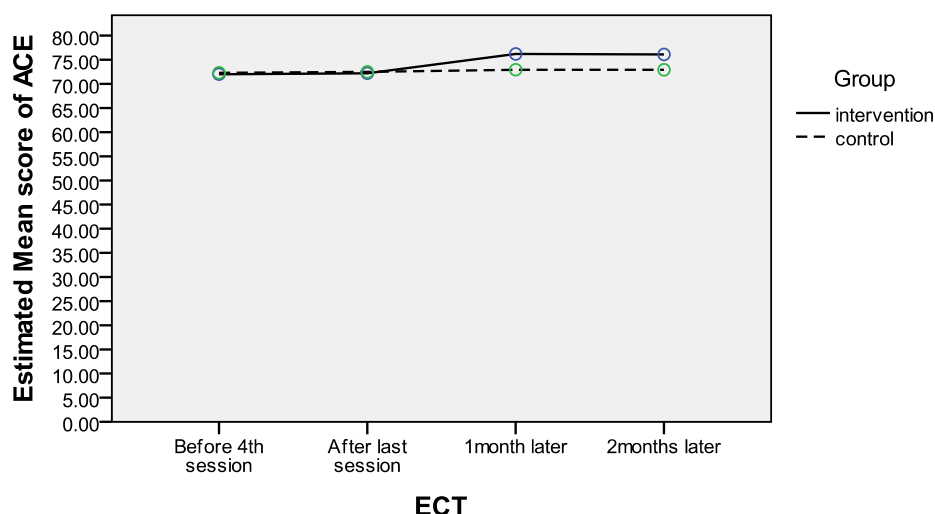
**Table 1. The characteristics and clinical aspects of the studied population in the intervention and placebo groups**

	Intervention group n = 36	Placebo group n = 38	p
Age (years)	37.8 ± 12.0	44.7 ± 13.1	0.02
Female/male (%)	47.2/52.8	50/50	0.8
Marital status (%)			
- Married	69.2	84.2	0.2
- Single	36.8	15.8	
Education (yrs)	10.0 ± 4.9	8.3 ± 4.5	0.1
ACE-R score	37.8 ± 12.1	44.7 ± 13.1	0.02
- Baseline	71.7 ± 14.2	72.6 ± 14.3	0.82
- After the 4 <sup>th</sup> session of ECT	71.7 ± 14.2	72.6 ± 14.3	0.91
- After last session of ECT	72.1 ± 14.1	72.6 ± 14.8	0.85
- One month after the last session of ECT	76.1 ± 13.3	73.0 ± 13.9	0.18
- Two months after the last session of ECT	76.4 ± 13.5	73.6 ± 13.7	0.12

Values are expressed as mean ± SD or percentage. ACE-R: Addenbrooke's Cognitive Examination-Revised; ECT: Electroconvulsive therapy

**Table 2. Addenbrooke's Cognitive Examination-Revised (ACE-R) scores in the patients before the 4th session, after the last session, and 1 and 2 months after the termination of electroconvulsive therapy (ECT) using repeated measures analysis of covariance**

		F-test	df	p
Main effects:	Time effect	6.55	(3,63)	0.001
	Intervention effect	2.28	(1,65)	0.136
	Interaction effect	5.45	(3,63)	0.002
Covariate effects:	Before the intervention	305.6	(1,65)	< 0.001
	Age	3.78	(1,65)	0.056
	Education	10.9	(1,65)	0.002



**Figure 1. Mean scores of Addenbrooke's Cognitive Examination-Revised (ACE-R) in the two groups during the course of study**  
**\*P-values less than 0.05 were observed in the intervention group between the scores one and two months after electroconvulsive therapy (ECT) and baseline and after the 4th and last sessions of ECT**

## DISCUSSION

In this study, the effects of a combination of 3 herbal foods on ECT-induced memory impairment were investigated among patients with mood disorders in Isfahan, Iran. The findings indicated that using this combination could have favorable effects on improving impaired memory, especially one or two months after the last ECT session. However, it had no significant effects during and immediately after the ECT period.

As mentioned, memory impairment due to ECT has been reported in many studies. It is thus considered as the most important barrier for common administration of ECT in the treatment of patients with mood disorders despite its beneficial effects.<sup>[3,4]</sup> Pharmacological approaches indicated that drugs such as donepezil and desmopressin can reduce memory deficits in patients after ECT.<sup>[7,8]</sup> Nevertheless, it seems that this group of patients, particularly in developing countries, prefer to use traditional medicine and have poor compliance with pharmacological agents. As a result, many recent studies have focused on developing new herbal drugs for this purpose. According to their findings, plant extracts and their bioactive components such as flavonoids, saponins, alkaloids, and glycosides have important effects on memory impairment mechanisms including cholinergic, gamma-aminobutyric acid releasing (GABAergic), glutaminergic, serotonergic, catecholaminergic, and histaminergic systems by enhancement of cerebral blood flow and elevation of ribonucleic acid (RNA) mainly because of antioxidant effects.<sup>[10]</sup>

In the current study, we investigated the effects of 3 herbal foods, i.e. CR, CS, and honey, on ECT-induced memory impairment. According to our cultural and Islamic reports, these compounds have significant effects in this field.<sup>[22]</sup> The most important effect of these 3 agents is their antioxidant capabilities. Evidence from many regional studies and other research throughout the world supports the mentioned effect. Accordingly, foods which have antioxidant potential have improved cognitive performance and memory scores in clinical studies.<sup>[23,24]</sup> The effects of other bioactive components should be evaluated in future studies.

In this study, we evaluated the effects of a combination of CR, CS, and honey on memory impairment. Iranian traditional and Islamic literature has reported the effects of these 3 foods on memory improvement.<sup>[25]</sup> However, we failed to find any similar published study on the effects of this combination therapy. We thus presented the related studies about each component separately.

The medical properties and antioxidant potency of CR have been confirmed in many studies.<sup>[15,16]</sup> CR is one of the components of Abana, an Indian Ayurvedic poly-herbal formula, which is prepared to enhance memory by reducing brain cholinergic activity.<sup>[26]</sup> In contrast, in one study in China on the ameliorating effects of some Chinese herbs on improving cognition in an animal model, CR did not have a significant effect in this field.<sup>[27]</sup>

The memory and cognitive enhancement effects of CS or saffron and Crocus have been approved in many

studies.<sup>[12,13]</sup> Many studies in Iran and other countries support and extend previous findings about the efficacy of CS in learning and memory mechanisms. With 80% of the world saffron originating from Iran (Khorassan province), its consumption in Iranian herbal medicine have been reported for various purposes.<sup>[28]</sup> Similarly, a Greek study showed that CS and crocins, one of active water-soluble components of CS, have an important role in recognition and memory.<sup>[13]</sup>

The medical benefits of honey have been proved by many experimental sciences. Accordingly, honey is a treatment as well as a food and has a wide range of bioactive properties.<sup>[17]</sup> Regarding memory, Chepulis et al. in New Zealand performed an animal study and indicated that consumption of honey could improve spatial memory in rats.<sup>[29]</sup>

All mentioned studies confirmed the memory enhancement effect of the studied herbal foods.

Though the ACE-R score was not significantly different between our two groups during the course of study (non-significant intervention effect), significant time and interaction effects were approved by significant increase of ACE-R scores one and two months after ECT in the intervention group. It is hence concluded that this herbal combination would be more effective one and two months after the ECT period. We did not study the mean scores of ACE-R 3 or 6 months after the ECT. However, it has been reported that memory impairment due to ECT, especially the retrograde amnesia, lasts for 6 months after ECT.<sup>[30]</sup> Further research with long duration is recommended to evaluate memory 3 to 6 months after ECT to obtain more conclusive results.

Most previous research on the anti-amnesic effects of herbal medicines was conducted on animals. In addition, the majority of available studies were from India or China.<sup>[9,27,31]</sup> The strength of our study was that we assessed patients, because the studied herbal foods are consumed regularly and have no adverse effect.

The limitations of this study were small sample size and the short duration of the herbal drug administration.

However, for better understanding of the usefulness of the mentioned herbal foods, further studies should be designed to determine the effects of each component separately. According to Vinekar et al., new scopes of research in attenuating ECT-induced amnesia, especially its retrograde form, should focus

on simplification of the formulation for better understanding of its related mechanisms.<sup>[32]</sup>

In summary, our findings confirmed previous evidence regarding the memory improving effects of CR, CS, and honey. Nonetheless, for achieving new insights about the underlying mechanisms of ECT-induced amnesia and its attenuation, the mentioned limitations and recommendations should be considered in future studies in this field.

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