



Original Research Paper

# Efficacy and safety of saffron as adjunctive therapy in adults with attention-deficit/hyperactivity disorder: A randomized, double-blind, placebo-controlled clinical trial

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## Highlights

Saffron might be beneficial in adults with ADHD.

Saffron may increase the efficacy of [Ritalin](#) in [treatment](#) of ADHD patients.

Saffron is a safe [treatment](#) for ADHD.

## Abstract

### Objective

Around 30% of patients with Attention-Deficit/Hyperactivity Disorder (ADHD) do not respond to [Ritalin](#) or cannot tolerate its side effects, which necessitates the consideration of alternative options. Previous studies have shown the beneficial effects of [Crocus sativus](#) (saffron) in children with ADHD. However, its potential therapeutic effects in adults with ADHD is unknown. This study aimed to evaluate the efficacy and safety of saffron as an adjuvant to Ritalin for improving symptoms in adults with ADHD.

### Design

This was a randomized, double-blind, placebo-controlled clinical trial.

### Methods

Fifty-six patients diagnosed with ADHD were assigned into two parallel groups to receive Ritalin (30 mg/day) plus placebo or Ritalin plus saffron (15 mg twice daily) for six weeks. The patients were assessed with Conners' [Adult ADHD](#) Rating Scales (CAARS) and the [Adult ADHD](#) Self-Report Scale (ASRS) at baseline, week 3 and week 6.

### Results

Forty-four patients completed the trial. GLM repeated-measure analysis demonstrated significant time  $\times$  treatment interaction effect for ASRS ( $df=2$ ,  $F=3.455$ , and  $P\text{-value}=0.036$ ) and CAARS ( $df=1.584$ ,  $F=3.939$ , and  $P\text{-value}=0.033$ ) score from baseline to the study endpoint. We found a significantly greater reduction in ASRS scores in the saffron group compared with the placebo group from baseline to the study endpoint (week 6) ( $P\text{-value}=0.024$ ). However, the change score from baseline to week 3 was not significantly different between trial groups ( $P\text{-value}=0.269$ ). There was no significant difference in the improvement of CAARS scores between saffron and placebo from baseline to week 3 or 6 ( $P\text{-value}=0.564$  and  $0.089$ , respectively). There was no significant difference between the two groups in baseline parameters and frequency of side effects.

### Conclusions

Saffron combination therapy with Ritalin can effectively improve symptoms of patients with ADHD. However, further studies with larger sample sizes and longer follow-up treatment are needed to confirm our findings.

This trial was registered with the Iranian Registry of [Clinical Trials](#) ([www.irct.ir](http://www.irct.ir); No IRCT20090117001556N111).

## Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a mental-behavioral disorder categorized by impulsive behavior, hyperactivity and inattentiveness that affects 4% of adults in various aspects of personal and social life [1], [2]. Studies have indicated the negative impact of ADHD on academic and occupational performance, family relationships, self-esteem and functional ability [3], [4], [5], [6]. The main underlying molecular mechanisms of ADHD are impaired dopaminergic and noradrenergic transmission [7]. Treatment of ADHD includes medication or behavioral therapy and a combination of both, which is documented to be more effective [8], [9]. The most common pharmacological choice for managing ADHD symptoms is methylphenidate (Ritalin) by inhibiting dopamine transporters and increasing the dopamine level in the neuronal synapses [10], [11]. Although Ritalin modifies the ADHD symptoms and improves cognitive deficits, it fails in some cases or associates with adverse effects like nausea, insomnia, transient headache, low appetite and behavioral rebound [8], [12], [13], [14], [15]. In this regard, several studies have focused on non-stimulant drugs as an alternative for ADHD treatment with fewer adverse effects. Among all medications, antidepressants were effective in treating ADHD [16] such as Bupropion in comparison with Ritalin [17], [18]. Despite the potency of antidepressants, the side effects like orthostatic hypotension, anticholinergic effects and arrhythmias limited their prescription [19]. Moreover, the use of stimulants such as Ritalin for the treatment of ADHD is often believed to cause dependence on stimulants or lead to a predisposition to the use of substances later on in life. Therefore, alternative approaches including non-stimulant agents and herbal medicine might be preferred by patients and their parents.

The use of alternative approaches, particularly herbal medicine for the treatment of various disorders dates back to hundreds of years ago. Herbal medicine is more readily accepted among populations worldwide due to cultural backgrounds and their safety profile compared to undesirable side effects of approved drugs [20]. More importantly, natural products or herbs are often fertile ground for discovering new drug candidates and the development of modern medicines [21]. For instance, *Hypericum perforatum* (more commonly known as St John's wort) is commonly used throughout Europe and has well-demonstrated antidepressant effects [22]. *Crocus sativus* is a traditional plant known for its culinary, coloring and medicinal features in Asian and European countries for years. The dried part of *Crocus sativus* (stigma), named saffron, possess the main role in the treatment of many diseases. The important bioactive constituents of saffron include Crocin, Picrocrocin, Safranal and Crocetin which are responsible for the intense red-orange color, bitter taste and odor, respectively [23] and have been considered as neuroprotective components [24]. Based on recent studies, saffron has antitumor, antispasmodic, antihypertensive, antiatherogenic, anticoagulant [25], antiseptic, antidepressant and anticonvulsant properties [26]. Interest in the evaluation of saffron's impact in the central nervous system (CNS) is increasing. Hence, saffron has been shown to be comparable to fluoxetine and imipramine for the treatment of mild to moderate depression [19], [27], [28], [29], [30]. Concomitantly, saffron components enhance the inhibition of dopamine and norepinephrine reuptake and play a role as N-methyl-D-aspartic acid receptor antagonist and GABA- $\alpha$  agonists [31]. Likewise, there is various evidence about saffron improving memory and ameliorating anxiety and depression [32], [33]. Saffron is believed to be of value as an antidepressant, and antidepressants have evident effects in improving ADHD symptoms [34], [35].

In this randomized, double-blinded, placebo-controlled clinical trial, we aimed to investigate the beneficial effects of saffron as an adjunctive treatment with Ritalin in adults with ADHD.

## Section snippets

### Trial design and settings

This is a randomized, double-blind, placebo-controlled clinical trial, conducted on adults with ADHD at the outpatient psychiatric clinic of Roozbeh Hospital (Tehran University of Medical Sciences, Tehran, Iran) from July 2018 to February 2020. This study was approved by the institutional review board (IRB) and the ethics committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1397.259). Also, this study was in accordance with the Declaration of Helsinki and its subsequent revision.

### Participants and baseline characteristics

Fig. 1 illustrates the flow diagram of this trial. A total of 106 ADHD patients were screened against the eligibility criteria, and 56 patients were included and randomized into two parallel groups receiving either Ritalin plus saffron ( $n = 28$ ) or Ritalin plus placebo ( $n = 28$ ). Within each group, six patients were excluded due to consent withdrawal (three in the saffron group and six in the placebo group), substance abuse (two in the saffron group), and emigration from the city (one in the

## Discussion

To the best of our knowledge, this is the first randomized, double-blinded clinical trial investigating the beneficial effects of saffron as an adjunctive treatment in adults with ADHD. The present randomized, double-blind, placebo-controlled clinical trial demonstrated that six weeks of adjuvant therapy with saffron and Ritalin improved ADHD symptoms in adults. Overall, our findings demonstrated that saffron adjunctive treatment led to greater improvement in ASRS and CAARS, i.e. primary

## Conclusion

Around 30% of patients with ADHD do not respond to Ritalin or cannot tolerate its side effects, necessitating the consideration of alternative options. In this randomized, double-blind, placebo-controlled clinical trial, we demonstrated that saffron combination therapy with Ritalin can effectively improve symptoms of patients with ADHD. However, the outcomes of this study must be considered preliminary and further studies with larger sample sizes and longer follow-up are needed to confirm our

## Ethical Statement

This study was approved by the institutional review board (IRB) and the ethics committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1397.259). Also, this study was in accordance with the Declaration of Helsinki and its subsequent revision. All patients provided

written informed consent, being aware of the procedure and purpose of the study and the possibility of leaving the trial and returning to their standard treatment without any problem concerning their relationship with

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## CRediT authorship contribution statement

Benyamin Pazoki, Nadia Zandi, Zeinab Assaf, Hossein Sanjari Moghaddam, Arefeh Zeinoddini participated in data acquisition analysis and preparation of the first draft of manuscript. Shahin Akhondzadeh and Mohammadreza Mohammadi designed the manuscript, provided the outlines for presentation of the study, supervised the study process and edited the final manuscript. All authors have reviewed the process of data analysis, commented on previous versions of the manuscript, and approved the final

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## Declarations of interest

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