• Meta-analysis

Saffron (*Crocus sativus* L.) and major depressive disorder: a meta–analysis of randomized clinical trials

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BACKGROUND: Due to safety concerns and side effects of many antidepressant medications, herbal psychopharmacology research has increased, and herbal remedies are becoming increasingly popular as alternatives to prescribed medications for the treatment of major depressive disorder (MDD). Of these, accumulating trials reveal positive effects of the spice saffron (*Crocus sativus* L.) for the treatment of depression. A comprehensive and statistical review of the clinical trials examining the effects of saffron for treatment of MDD is warranted.
OBJECTIVE: The purpose of this study was to conduct a meta-analysis of published randomized controlled trials examining the effects of saffron supplementation on symptoms of depression among participants with MDD.
SEARCH STRATEGY: We conducted electronic and non-electronic searches to identify all relevant randomized, double-blind controlled trials. Reference lists of all retrieved articles were searched for relevant studies.
INCLUSION CRITERIA: The criteria for study selection included the following: (1) adults (aged 18 and older) with symptoms of depression, (2) randomized controlled trial, (3) effects of saffron supplementation on depressive symptoms examined, and (4) study had either a placebo control or antidepressant comparison group.
DATA EXTRACTION AND ANALYSIS: Using random effects modeling procedures, we calculated weighted mean effect sizes separately for the saffron supplementation *vs* placebo control groups, and for the saffron supplementation *vs* antidepressant groups. The methodological quality of all studies was assessed using the Jadad score. The computer software Comprehensive Meta-analysis 2 was used to analyze the data.
RESULTS: Based on our pre-specified criteria, five randomized controlled trials (n = 2 placebo controlled trials, n = 3 antidepressant controlled trials) were included in our review. A large effect size was found for saffron supplementation *vs* placebo control in treating depressive symptoms (M ES = 1.62, P < 0.001), revealing that saffron supplementation significantly reduced depression symptoms compared to the placebo control. A null effect size was evidenced between saffron supplementation and the antidepressant groups (M ES = −0.15) indicating that both treatments were similarly effective in reducing depression symptoms. The mean Jadad score was 5 indicating high quality of trials.
CONCLUSION: Findings from clinical trials conducted to date indicate that saffron supplementation can improve symptoms of depression in adults with MDD. Larger clinical trials, conducted by research teams outside of Iran, with long-term follow-ups are needed before firm conclusions can be made regarding saffron's efficacy and safety for treating depressive symptoms.
KEYWORDS: *Crocus*; depressive disorder; dietary supplements; mood disorders; quality of life; medicine, herbal; meta-analysis

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1 Introduction

Depression is one of the most commonly diagnosed psychological disorders. Approximately 1 in 5 adults report experiencing one episode of depression in their lifetime, with women being twice as likely to develop depression[1]. Symptoms of major depressive disorder (MDD) include excessive weight loss or gain, sleepiness or insomnia, feelings of worthlessness, anhedonia, difficulty in thinking and concentrating, a persistent sad mood, and thoughts of suicide or death for a two-week period or longer[2,3]. There is a high rate of comorbid symptoms of MDD for individuals with chronic illnesses, such as heart disease, hormonal disorders, Parkinson's disease, diabetes, and Alzheimer's disease[4]. Reviews by Kessler and his colleagues have found that MDD is associated with an enormous economic burden, the largest component of which is drawn from lost work productivity due to depression[5].

Although many treatment approaches exist, pharmacotherapy is currently the most commonly used outpatient treatment for depression[6,7]. Findings from a recent meta-analysis examining the safety and tolerability of antidepressant medications indicate that the effectiveness of these medications are related to the severity of depression symptoms, and that antidepressant medications provide minimal benefits compared to placebo for patients with mild to moderate depressive symptoms. Additionally, many patients cannot tolerate the side effects (*e.g.*, anxiety, loss of appetite, and sexual dysfunction) associated with some antidepressant medications, do not respond adequately, or develop tolerance through the course of the treatment with medication[8]. There is currently a need for more effective and less risky treatments for depression.

Due to safety concerns and side effects of many antidepressant medications, herbal psychopharmacology research has increased, and herbal remedies are becoming increasingly popular as alternatives to prescribed medications for the treatment of MDD in the last several years[9]. Of these, the spice saffron (from the indigenous southwest Asian plant *Crocus sativus* L.) has emerged as a promising herbal compound for the treatment of depression based on findings from recent clinical trials[10]. Although saffron is propagated in several regions, Iran produces about 90% of the world's saffron and generates most of the research into its potential medical uses.

Similar to antidepressants, saffron may exert its antidepressant effect by modulating the levels of certain chemicals in the brain, including serotonin (a mood-elevating neurotransmitter). Although it has been proposed that saffron increases serotonin levels in the brain[11,12], the exact mechanism of action for this is unknown. More specifically, saffron extract might inhibit serotonin reuptake in synapses. Inhibiting synaptic serotonin reuptake keeps serotonin in the brain longer, thereby enhancing its positive effects while combating depression. This proposed mechanism is supported by animal studies, which demonstrated antidepressant properties in extracts sourced from multiple parts of the saffron plant[11,12]. These medicinal properties of saffron may be attributed to a number of its compounds such as crocetin, crocins, and safranal, which have strong antioxidant and radical scavenger properties to protect against a variety of reactive radical oxygen species and pro-inflammatory cytokines. However, the specific components of saffron that affect mood states and improve symptoms of depression have not been identified.

Although accumulating evidence supports the use of saffron for the treatment of depression[13,14], the effects of saffron on depressive symptoms have not been comprehensively and statistically reviewed. Thus, the purpose of this article was to meta-analytically review randomized clinical trials, which examined the effects of saffron supplementation on depressive symptoms compared to a control group, *i.e.*, placebo control or antidepressant control groups, in adults with symptoms of MDD.

2 Methods

2.1 Search strategy

To ensure the rigor of our systematic review and meta-analysis, we designed and reported our findings using a checklist of items in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" statement as far as possible[15]. We were unable to obtain a PRISMA registration number, because we attempted to register following completion of our review.

To avoid bias retrieval of searching only major journals and to obtain grey literature (*e.g.*, abstracts, unpublished studies[16]), we used the following five search strategies. First, two independent reviewers searched the following electronic databases: Allied and Complementary Medicine Database, Cumulative Index to Nursing and Allied Health Literature, The Cochrane Library, EMBASE, MEDLINE, PubMed, and Web of Science. The key terms outlined by Ulbricht and colleagues were used to search titles and abstracts[17]. Second, ancestry searches, *i.e.*, treeing backward, were conducted using the references lists of all clinical studies, which met our inclusion criteria[17]. Third, we contacted active researchers in the field to retrieve either current or unpublished research. Fourth, computerized author database searches were conducted on all authors of retrieved studies meeting the inclusion criteria. Finally, manufacturers of commercial saffron products were contacted to identify published research material. Only articles published in English were reviewed and our search was from journal inception until April 2013.

2.2 Inclusion and exclusion criteria

The criteria for study selection included the following: (1) adults (aged 18 and older) with symptoms of depression, (2) randomized controlled trial, (3) effects of saffron supplementation on depressive symptoms examined, and (4) study had either a placebo control or antidepressant comparison group. Based on their abstracts, the studies, which appeared to meet the criteria, were independently considered for inclusion by all the co-authors. Disagreements among the co-authors were resolved through discussion. A study was included if all reviewers agreed that it met the inclusion criteria. Based on this strategy, 21 studies were identified; 15 studies were excluded because the participants did not report having depressive symptoms. As well, one study was excluded because it did not have either a placebo control or antidepressant comparison group, *i.e.*, this trial compared the effects of saffron petal *vs* stigma on depressive symptoms[18]; five trials met our inclusion criteria and thus were included in this meta-analytic review[19-23]. Informed consent was obtained from all the participants in the five reviewed trials, and the protocols satisfied the Ethics Committee requirements of all research centers in which the studies were conducted.

2.3 Meta-analytic procedures

Using random effects modeling procedures, we calculated weighted mean effect sizes separately for the saffron supplementation *vs* placebo control groups, and for the saffron supplementation *vs* antidepressant (*e.g.*, fluoxetine and imipramine) groups and performed corrections for sample-size bias to estimate d[24]. We used Hedges and Olkin's procedures[25] to correct for sample-size biases. To derive effect sizes for within-subject studies, the correlation (r) between posttest and pretest measures was needed. Unfortunately, values of r are not reported in studies when the primary research studies do not investigate relationships between measures. None of the studies in this synthesis reported r. We attempted to contact the corresponding authors of the articles included in our review; however, none responded to the request for this information. Thus, we used a conservative value of $r = 0.50$ to estimate the correlation between pretest and posttest values on measures of depression. Positive effect sizes represent a positive effect for saffron supplementation on symptoms of depression *vs* the comparison group. Along with the weighted average effect sizes, we computed the 95% confidence intervals (CIs). If the CI did not include zero, then the mean effect size was statistically significant at the $P < 0.05$ level. The I^2 statistic was used to assess for statistical heterogeneity amongst studies. We also graphed a forest plot (available upon request from the first author), which showed each study as a point estimate bounded by its confidence intervals. The methodological quality of all included studies was assessed by using a quality assessment checklist adapted from the Consolidated Standard of Reporting Trials (CONSORT) guidelines[26]. As well, we computed the Jadad score to assess the quality of the clinical trials[27]. The computer software Comprehensive Meta-analysis 2 was used to analyze the data.

3 Results

3.1 Descriptive information

Based on the search strategies described above, five randomized controlled trials were identified that examined the effects of saffron on depression symptoms and met our inclusion criteria. See Figure 1 of the flow diagram for study selection. See Tables 1 and 2 for a summary of key details of these studies. The Structured Clinical Interview for DSMI-IV Axis I Disorders (SCID) for MDD as well as a baseline score of 18 or higher on the Hamilton Depression Rating Scale was used to determine depressive symptomatology in participants. Trials ranged from 6 to 8 weeks, and all the trials used a 30 mg/d dose of saffron.

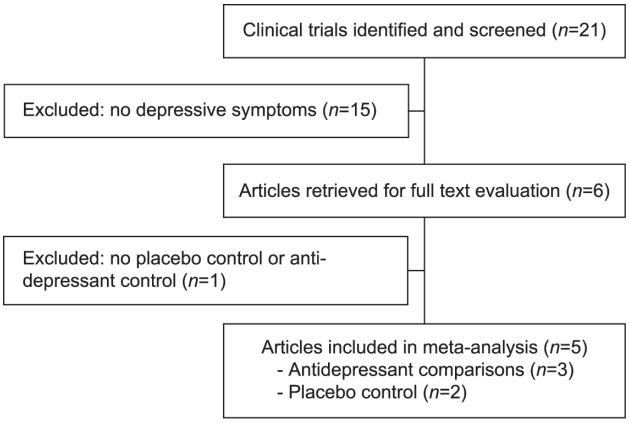

Figure 1 Flow diagram for study selection

3.2 Effect size information, adverse events, and study quality

A null effect size was found for saffron supplementation *vs* antidepressant (*i.e.*, fluoxetine and imipramine (M ES = −0.15, 95% CI: −0.52-0.22, $P = 0.42$, $n = 3$ ES). The I^2 statistic was 0%, which indicates no heterogeneity amongst the studies. A large effect size was found for saffron supplementation *vs* placebo control (M ES = 1.62, 95% CI: 1.10-2.14, $P < 0.001$, $n = 2$; $I^2 = 0$). The I^2 value of 0% indicates no observed heterogeneity. None of the trials reported any severe adverse events associated with the use of saffron supplementation. The most common adverse effects reported for saffron supplementation were headache, nausea, anxiety, and decreased appetite (see Table 3 for a detailed description of the adverse events reported by group). The Jadad score for all the trials included in our review was 5 indicating high quality of trials.

Table 1 Summary of clinical trials examining effects of saffron supplementation on patients with major depression

First author (year)	Design	Participants	Treatment group	Control/ comparison group	Main results	Number of adverse events (saffron *vs* control/ comparison group)	ES data
Akhondzadeh (2005)[19]	Six-week double-blind, placebo-controlled	$N = 35$; M age = 36.3	Saffron capsule (30 mg/d) (stigma)	Placebo capsule	Saffron had better outcome on HDRS	18 *vs* 10	ES = 1.51, CI: 0.81-2.21, Z value = 4.22, $P < 0.001$
Akhondzadeh Basti (2007)[20]	Six-week double-blind randomized	$N = 38$; M age = 34.8	Saffron capsule (30 mg/d) (petal)	Fluoxetine (20 mg/d)	Saffron and fluoxetine similarly effective in improving HDRS	18 *vs* 41	ES = –0.05, CI: –0.67-0.56, Z value = –0.36, $P = 0.86$
Moshiri (2006)[21]	Six-week double-blind, placebo controlled, randomized	$N = 36$; M age = 35.65	Saffron capsule (30 mg/d) (petal)	Placebo capsule	Saffron had better improvement on HDRS scores than control	29 *vs* 13	ES = 1.75, CI: 0.97-2.51, Z value = 4.45, $P < 0.001$
Noorbala (2005)[22]	Six-week double-blind randomized	$N = 38$; M age = 36.9	Saffron capsule (30 mg/d) (stigma)	Capsule of fluoxetine (20 mg/d)	Both groups similarly effective in treating depression	16 *vs* 34	ES = –0.15, CI: –0.73-0.50, Z value = 0.43, $P = 0.71$
Akhondzadeh (2004)[23]	Six-week double-blind randomized trial	$N = 30$; M age = 34	Saffron capsule (30 mg/d)	Imipramine (100 mg/d)	Saffron and imipramine similarly effective in improving HDRS	18 *vs* 33	ES = –0.33, CI: –1.05-0.38, Z value = –0.90, $P = 0.38$

N: number of participants who completed the trial; *M* age: mean age of the participants; CI: 95% confidence intervals; HDRS: Hamilton Depression Rating Scale; positive effect size (ES): saffron group performed better than control/comparison group.

4 Discussion

The purpose of this study was to use meta-analytic techniques to determine the magnitude of effects of saffron supplementation on depressive symptoms in clinical trials conducted on participants with MDD. This review revealed that saffron may be helpful for treating depressive symptoms among individuals with MDD. In the two studies[19,21] that examined the effects of saffron supplementation *vs* placebo control groups, a large effect size was found in favor of saffron supplementation. For the three studies[20,22,23] that examined the effects of saffron supplementation compared to antidepressant groups (*i.e.*, fluoxetine or imipramine), significant improvements in depressive symptoms were observed among participants in both conditions. No significant differences were observed, however, in the reduction in depressive symptoms between participants in the saffron and the antidepressant conditions. In one study, there were a greater number of adverse effects associated with the use of the antidepressant medication imipramine as compared to saffron[23]. Taken together, the findings of the trials included in this meta-analysis indicate that saffron is an efficacious strategy for treating MDD in the short-term use.

In all of the trials reviewed, adverse events including headaches and nausea were frequently reported. In the two studies that compared saffron to a placebo, there were not significant differences in adverse events. Given the short duration of clinical trials to date (*i.e.*, 6 to 8 weeks), long-term effects are currently unknown. It remains to be determined how safe this nutritional supplement is for long-term use.

Although all the trials found improvements in depression scores following saffron supplementation, design limitations existed. Specifically, the five studies included in this meta-analytic review were single-center trials conducted within the same clinical setting in Iran, with short-term (6-8 weeks), used fixed saffron dosages, had small sample sizes (n = 30-38), used only one depression measure (*i.e.*, Hamilton Depression Rating Scale), had no follow-up assessments, pro-

Table 2 Methodological characteristics of included studies

First author (year)	Gender M/F	Randomization appropriate	Allocation concealed	Groups similar at baseline	Similar follow-up of groups	Outcome assessor blinded	Care provider blinded	Patients blinded	Attrition (*n*)	ITT analysis
Akhondzadeh (2005)[19]	+	+	+	+	+, short	+	+	+	5 (1 saffron, 4 placebo)	+
Akhondzadeh Basti (2007)[20]	+	+	+	+	+, short	+	+	+	2 (one from each group)	+
Moshiri (2006)[21]	+	+	+	+	+, short	+	+	+	4 (1 *C. sativus*, 3 placebo)	+
Noorbala (2005)[22]	+	+	+	+	+, short	+	+	+	2 (1 saffron, 1 fluoxetine)	+
Akhondzadeh (2004)[23]	+	+	+	+	+, short	+	+	+	0	−

ITT: intention-to-treat; M/F: male/female; +: yes, −: no.

Table 3 Type of adverse event reported by group

Adverse event	Saffron	Placebo control	Antidepressant comparison
Headache*	14	3	13
Nausea*	14	3	9
Anxiety*	18	3	14
Decreased appetite*	15	4	9
Stomach pain	4	2	0
Tremor	5	1	9
Sweating	4	1	6
Heart pounding	7	2	2
Increased appetite	12	1	10
Sedation	2	2	6
Hypomania	4	1	1
Dry mouth	1	0	7
Constipation	2	0	5
Urinary retention	1	0	5
Sexual dysfunction	3	0	9
Insomnia	3	0	3

*Highlighted side effects appeared in all 5 studies.

vided limited descriptive information on participants (*e.g.*, no studies reported SES, marital status, or education level), and lacked moderator analyses. The small sample sizes, however, most likely precluded the examination of important moderator variables (*e.g.*, gender and age). Previous reviews of saffron and other herbal medicines appear to recognize these limitations and have encouraged institutions in other countries to validate their research[9]. As well, further research is needed to determine the antidepressant mechanisms of action of saffron in humans. Using animal models, research suggests that reuptake inhibition of monoamines, *N*-methyl-D-aspartate antagonism, and improved brain-derived neurotrophic factor signaling may be mechanistic factors[28]. Remission of MDD is difficult to achieve with less than 50% of patients responding to standard treatments (*e.g.*, antidepressants). For patients who are not responding adequately to an antidepressants, the two main current treatment approaches are switching drugs or trying alternative approaches such as herbal medicine[13].

Preliminary research also reveals that saffron supplementation may be effective for improving depressive symptoms in non-clinically depressed populations. For example, in a secondary analysis, Agha-Hosseini *et al*[29] found that 8 weeks of saffron supplementation resulted in significant improvements in depression scores, compared to the placebo control group, in women with regular menstrual cycles who experienced premenstrual syndrome. Psychological issues, such as emotional distress and depression, are common symptoms of premenstrual syndrome[30,31].

In summary, while the antidepressant effects of saffron versus a non-saffron comparison group have been studied scientifically in five clinical trials, further studies yielding high quality data regarding saffron's safety, effectiveness, and mechanism of action are needed. As well, further data will enable a more detailed understanding of publication bias and potential moderator variables. Of importance, in trials testing the effects of imipramine and fluoxetine on symptoms of depression, no significant differences were found between saffron and the antidepressant medications in terms of improvements in depressive symptoms. Although the studies reviewed have revealed sound scientific evidence for saffron as a possible depression treatment, the short

duration, use of a single self-report measure, lack of specific data on saffron's mechanism of action, and small sample sizes prevent us from drawing firm conclusions about the effects of saffron on depression. While findings of improved mental health combined with excellent short-term safety profile suggest saffron may be an effective alternative approach for the treatment of MDD, it is currently unknown if findings from initial trials will translate into long-term health benefits until well-controlled, longer-term studies are performed. Large-scale, multi-site trials conducted in line with the CONSORT guidelines are needed to clarify saffron's potential role, safety profile, and mechanisms of action for the treatment of MDD.

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6 Competing interests

Drs. Anton and Hausenblas serve as scientific advisors and as consultants for the company ReBody, LLC., which is an affiliate of Reserve Life Organics, LLC. d/b/a Reserveage Organics, the developer and marketer of a product in which saffron is used. Neither author has received personal financial gain from sales of this product. All findings and views expressed in this paper are those of the authors and do not necessarily reflect the views of the Reserve Life Organics, LLC., d/b/a Reserveage Organics that funded this trial.

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