HHS Public Access

Author manuscript

J Integr Med. Author manuscript; available in PMC 2015 November 13.

Published in final edited form as:

J Integr Med. 2013 November ; 11(6): 377–383. doi:10.3736/jintegrmed2013056.

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

Heather Ann Hausenblas, Ph.D.[1], **Debbie Saha, B.S.**[2], **Pamela Jean Dubyak, M.S.**[3], and **Stephen Douglas Anton, Ph.D.**[4]

[1]Associate Professor, Jacksonville University, Jacksonville, 32211; Adjunct Professor, University of Florida, Gainesville, 32611

[2]Research Assistant, University of Florida, Gainesville, 32611; Graduate Student, University of South Florida, Tampa, 33620

[3]Graduate Student, University of Florida, Gainesville, 32611

[4]Assistant Professor & Clinical Research Division Chief, University of Florida, Gainesville, 32611

Abstract

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 anti-depressant 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

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.

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 condition. A null effect size was evidenced between saffron supplementation vs. 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 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

saffron; depression; dietary supplement; mood disorders; quality of life; review; psychiatric; herbal medicine

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 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 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]. 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 anti-depressant 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 anti-depressant 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 the saffron petal vs. the 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 (i.e., 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 $r = .50$ 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 (CI). If the confidence interval did not include zero, then the mean effect size was statistically significant at the $p < .05$ 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 Table 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.

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 trials.

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 that examined the effects of saffron supplementation versus placebo control groups, a large effect size was found in favor of saffron supplementation. For the three studies 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. 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 group, 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, short-term (6 – 8 weeks), use fixed saffron dosages, had small sample sizes (N = 30 – 42), used only one depression measure (i.e., Hamilton Depression Rating Scale), had no follow-up assessments, provided 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 (NMDA) 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 anti-depressant, 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[29]. 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 on 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.

Acknowledgments

Support was provided by the University of Florida Claude D. Pepper Older Americans Independence Center (NIH/NIA P30AG028740) and Clinical and Translational Science Institute (NIH/NCRR UL1TR000064). Stephen Anton is supported by a K23 AT004251-01A2, an Early Career Investigator Award from the American Heart Association (09CRP2390173), and Thomas H. Maren Foundation.

References

1. Hirschfeld R. Depression epidemiology and its treatment evolution. J Clin Psychiatry. 2012; 73(10):e29–e29. [PubMed: 23140659]
2. Maj M. Development and validation of the current concept of major depression. Psychopathology. 2012; 45(3):135–146. [PubMed: 22399134]
3. Maj M. Validity and clinical utility of the current operational characterization of major depression. Int Rev Psychiatry. 2012; 24(6):530–537. [PubMed: 23244608]
4. González H, Tarraf W. Comorbid cardiovascular disease and major depression among ethnic and racial groups in the United States. Int Psychogeriatr. 2013; 25(5):833–841. [PubMed: 23290766]
5. Kessler R, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003; 289(23):3095–3105. [PubMed: 12813115]
6. Olfson M, Marcus S, Druss B, Elinson L, Tanielian T, Pincus H. National trends in the outpatient treatment of depression. JAMA. 2002; 287(2):203–209. [PubMed: 11779262]
7. Williams JJ, Rost K, Dietrich A, Ciotti M, Zyzanski S, Cornell J. Primary care physicians' approach to depressive disorders. Effects of physician specialty and practice structure. Arch Fam Med. 1999; 8(1):58–67. [PubMed: 9932074]
8. Ferguson J. SSRI antidepressant medications: adverse effects and tolerability. Prim Care Companion. J Clin Psychiatry. 2001; 3(1):22–27. [PubMed: 11229450]
9. Sarris J, Panossian A, Schweitzer I, Stough C, Scholey A. Herbal medicine for depression, anxiety and insomnia: a review of psychopharmacology and clinical evidence. Eur Neuropsychopharmacol. 2011; 21(12):841–860. [PubMed: 21601431]
10. Dwyer A, Whitten D, Hawrelak J. Herbal medicines, other than St. John's Wort, in the treatment of depression: a systematic review. Altern Med Rev. 2011; 16(1):40–49. [PubMed: 21438645]
11. Georgiadou G, Tarantilis P, Pitsikas N. Effects of the active constituents of Crocus Sativus L., crocins, in an animal model of obsessive-compulsive disorder. Neurosci Lett. 2012; 528(1):27–30. [PubMed: 22985509]
12. Wang Y, Han T, Zhu Y, Zheng CJ, Ming QL, Rahman K, Qin LP. Antidepressant properties of bioactive fractions from the extract of Crocus sativus L. J Nat Med. 2010; 64(1):24–30. [PubMed: 19787421]
13. Kamalipour M, Jamshidi AH, Akhondzadeh S. Antidepressant effect of Crocus sativus: An evidence based review. Journal of Medicinal Plants. 2010; 9(6):35–38.
14. Modabbernia A, Akhondzadeh S. Saffron, passionflower, valerian and safe for mental health. Psychiatr Clin N Am. 2013; 36(1):85–91.
15. Moher D, Liberati A, Tetzlaff J, Altman D. the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009; 151(4): 264–269. [PubMed: 19622511]
16. Conn VS, Valentine JC, Cooper HM, Rantz MJ. Grey literature in meta-analyses. Nursing research. 2003; 52(4):256–261. [PubMed: 12867783]
17. Ulbricht C, Conquer J, Costa D, Hollands W, Iannuzzi C, Isaac R, Jordan JK, Ledesma N, Ostroff C, Serrano JMG, Shaffer MD, Varghese M. An evidence-based systematic review of saffron (Crocus sativus) by the Natural Standard Research Collaboration. J Diet Suppl. 2011; 8(1):58–114. [PubMed: 22432635]
18. Akhondzadeh Basti A, Ghoreishi SA, Noorbala AA, Akhondzadeh SH, Rezazadeh SH. Petal and stigma of Crocus sativus L. in the treatment of depression: a pilot double - blind randomized trial. Journal of Medicinal Plans. 2008; 7(4):29–36.

19. Akhondzadeh S, Tahmacebi-Pour N, Noorbala A, Amini H, Fallah-Pour H, Jamshidi AH, Khani M. Crocus sativus L. in the treatment of mild to moderate depression: a double-blind, randomized and placebo-controlled trial. Phytother Res. 2005; 19(2):148–151. [PubMed: 15852492]
20. Akhondzadeh Basti A, Moshiri E, Noorbala A, Jamshidi A, Abbasi SH, Akhondzadeh S. Comparison of petal of Crocus sativus L. and fluoxetine in the treatment of depressed outpatients: a pilot double-blind randomized trial. Prog Neuropsychopharmacol Biol Psychiatry. 2007; 31(2): 439–442. [PubMed: 17174460]
21. Moshiri E, Basti AA, Noorbala AA, Jamshidi AH, Abbasi SH, Akhondzadeh S. Crocus sativus L. (petal) in the treatment of mild-to-moderate depression: a double-blind, randomized and placebo-controlled trial. Phytomedicine. 2006; 13(9–10):607–611. [PubMed: 16979327]
22. Noorbala AA, Akhondzadeh S, Tahmacebi-Pour N, Jamshidi AH. Hydro-alcoholic extract of Crocus sativus L. versus fluoxetine in the treatment of mild to moderate depression: a double-blind, randomized pilot trial. J Ethnopharmacol. 2005; 97(2):281–284. [PubMed: 15707766]
23. Akhondzadeh S, Fallah-Pour H, Afkham K, Jamshidi A, Khalighi-Cigaroudi F. Comparison of Crocus sativus L. and imipramine in the treatment of mild to moderate depression: a pilot double-blind randomized trial [ISRCTN45683816]. BMC Complement Altern Med. 2004; 4(1):12. [PubMed: 15341662]
24. Morris S. Estimating effect sizes from pretest-posttest-control group designs. Organizational Research Methods. 2008; 11(2):364–386.
25. Hedges, L.; Olkin, I.; Statistiker, M. Statistical methods for meta-analysis. Academic Press; New York: 1985.
26. Altman D, Schulz K, Moher D, Egger M, Davidoff F, Elbourne D, Gotzsche PC, Lang T. CONSORT Group. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med. 2001; 134(8):663–694. [PubMed: 11304107]
27. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials. 1996; 17(1):1–12. [PubMed: 8721797]
28. Berger F, Hensel A, Nieber K. Saffron extract and trans-crocetin inhibit glutamatergic synaptic transmission in rat cortical brain slices. Neuroscience. 2011; 180:238–247. [PubMed: 21352900]
29. Agha-Hosseini M, Kashani L, Aleyaseen A, Ghoreishi A, Rahmanpour H, Zarrinara AR, Akhondzadeh S. Crocus sativus L. (saffron) in the treatment of premenstrual syndrome: a double-blind, randomised and placebo-controlled trial. BJOG. 2008; 115(4):515–519. [PubMed: 18271889]
30. Joshi J, Pandey S, Galvankar P, Gogate J. Prevalence of premenstrual symptoms: Preliminary analysis and brief review of management strategies. J Midlife Health. 2010; 1(1):30–34. [PubMed: 21799636]
31. Tschudin S, Bertea P, Zemp E. Prevalence and predictors of premenstrual syndrome and premenstrual dysphoric disorder in a population-based sample. Arch Womens Ment Health. 2010; 13(6):485–494. [PubMed: 20449618]

J Integr Med. Author manuscript; available in PMC 2015 November 13.

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	# of Adverse Events Saffron vs Control/ Comparison Group	ES Data
Akhondzadeh (2004)[19]	6 wk double-blind randomized trial	*N* = 30 *M* age = 34	Saffron capsule (30mg/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* = .38
Akhondzadeh (2005)[24]	6 wk double-blind, placebo-controlled	*N* = 35 *M* age = 36.3	Saffron capsule (30mg/d) {stigma}	Capsule placebo	Saffron had better outcome on HDRS	18 vs 10	ES = 1.51, CI: 0.81, 2.21, *Z* value = 4.22, *p* < .001
Akhondzadeh Basti (2007)[25]	8 wk 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* = .86
Moshiri (2006)[27]	6 wk 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* < .001
Noorbala (2005)[28]	6 wk double-blind randomized	*N* = 38 *M* age = 36.9	Saffron capsules (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

Participants = number of participant who completed the trial. CI = 95% confidence intervals.

Note. Positive effect size (ES) =saffron group performed better than control/comparison group

Table 2

Methodological characteristics of included studies

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 (2004)[19]	+	+	+	+	+, short	+	+	+	0	−
Akhondzadeh (2005)[24]	+	+	+	+	+, short	+	+	+	5 (1 saffron, 4 placebo)	+
Akhondzadeh Basti (2007)[25]	+	+	+	+	+, short	+	+	+	2 (one from each group)	+
*Akhondzadeh Basti (2008)[26]	+	+	+	+	−	+	+	+	2 (one from each group)	+
Moshiri (2006)[27]	+	+	+	+	+, short	+	+	+	4 (1 C. sativus, 3 placebo)	+
Noorbala (2005)[28]	+	+	+	+	+, short	+	+	+	2 (1 saffron, 1 fluoxetine)	+

ITT (intention to treat), M/F: Men/Women

Symbols: + = yes, − = no; ? = unclear

Table 3

Type of Adverse Event Reported by Group

Adverse Event	Saffron	Placebo Control	Anti-depressant 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.