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Effect of saffron supplementation on symptoms of depression and anxiety: a systematic review and meta-analysis

Wolfgang Marx, Melissa Lane, Tetyana Rocks, Anu Ruusunen, Amy Loughman, Adrian Lopresti, Skye Marshall, Michael Berk, Felice Jacka, and Olivia M. Dean

Context: Saffron (*Crocus sativus* L.) has gained interest as a potential treatment in psychiatry. **Objective:** This systematic review and meta-analysis sought to investigate the effect of saffron supplementation, as both an adjunctive therapy and monotherapy, on symptoms of depression and anxiety in clinical and general populations compared with pharmacotherapy or placebo. **Data sources:** Using the PRISMA guidelines, a systematic literature review of randomized controlled trials was conducted. **Data extraction:** A meta-analysis was conducted to determine treatment effect. Risk of bias was assessed using the Jadad scale. **Results:** Twenty-three studies were included. Saffron had a large positive effect size when compared with placebo for depressive symptoms ($g = 0.99$, $P < 0.001$) and anxiety symptoms ($g = 0.95$, $P < 0.006$). Saffron also had a large positive effect size when used as an adjunct to antidepressants for depressive symptoms ($g = 1.23$, $P = 0.028$). Egger's regression test found evidence of publication bias. **Conclusions:** Saffron could be an effective intervention for symptoms of depression and anxiety; however, due to evidence of publication bias and lack of regional diversity, further trials are required. PROSPERO registration CRD42017070060.

INTRODUCTION

Saffron (*Crocus sativus* L.) and its constituents, including crocin, crocetin, and safranal, may have a positive effect on several neurobiological mechanisms implicated in mental illness.^{1–3} In animal models, whole saffron and implicated compounds have been reported to modulate pathways related to neurotransmitters,

immune regulation, inflammation, oxidative stress, the hypothalamus-pituitary-adrenal (HPA) axis, and neurotrophins.⁴ For example, in rats, the administration of a saffron extract dose-dependently increased brain concentrations of dopamine and, at high doses, increased glutamate levels.⁵ In another study, the administration of crocin modulated serotonergic activity in rats exposed to the nonselective serotonin receptor agonist

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Key words: depression, herbal medicine, inflammation, mental health, mood disorder, nutraceutical, saffron, treatment.

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meta-chlorophenylpiperazine, lowering obsessive-like behaviors.⁶ Saffron constituents also have anti-inflammatory, immune-regulating, and antioxidant properties, including the modulation of endogenous antioxidant enzymes.^{7–11} In addition, studies using animal stress models have confirmed that saffron modulates HPA axis activity by reducing plasma corticosterone concentrations.^{12,13} Finally, support for the neuroprotective effects of saffron and its constituent, crocin, is derived from studies demonstrating positive effects on the neurotrophin, brain-derived neurotrophic factor (BDNF) in animal stress models.^{14,15}

Two previous meta-analyses have reported saffron supplementation to improve measures of depression in clinical trials.^{16,17} Previous meta-analyses on this topic, however, have only examined the effects of saffron on depression in clinical populations with mild to major depression.^{16,17} Furthermore, since the publication of these reviews, several published intervention studies have been conducted in both depression and other mental illnesses. Therefore, using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, this systematic review and meta-analysis of randomized controlled trials (RCTs) aims to examine the transdiagnostic effects of saffron supplementation (as a stand-alone or adjunctive intervention) on symptoms of mental illness in both clinical and general populations compared with pharmacotherapy or placebo.

METHODS

Literature search

This review was written in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement (see [Appendix S1](#) in the Supporting Information online)¹⁸ and was prospectively registered on PROSPERO (CRD42017070060). A search strategy was developed based on the research question ([Table 1](#)). Studies were identified using the following databases: Medline (Pubmed), PsychInfo, Embase, the Cochrane Library, and CINAHL. Search terms were related to saffron and its constituents (“saffron” OR “crocus” OR “crocin” OR “crocin”) and mental health outcomes (“depression” OR “depressive disorder” OR “anxiety disorders” OR “affective symptoms” OR anxi* OR mood OR “psychological symptoms” OR “psychological distress”). The search strategy identified articles published since journal inception up to March 2018.

Studies were required to be RCTs, including crossover studies; be published in English; include measures

of mental health (eg, depression, low mood, depressive symptoms, emotional problems, and anxiety); and use any component of saffron (eg, whole saffron, standardized extracts, parts of saffron, or specific saffron-derived compounds). Interventions that included saffron in combination with standard medications were included; however, combined interventions with other novel ingredients were excluded. No limit on age or population was included, and the comparator could be either placebo or pharmacotherapy.

Data extraction

Two authors independently screened individual studies in duplicate, with disagreements resolved by consensus or a third author. Using a standardized and piloted extraction form, the following parameters were extracted from included studies: author/date, study design, sample size, total study period, population characteristics (including age, sex, and comorbidities), intervention characteristics (including dose, type, and duration of exposure, concomitant treatment), length of follow-up, adverse events, and mental health-related outcomes, including measures of depression, anxiety, mood. Outcomes not related to mental health were not extracted for this review.

Assessment of study risk of bias

Risk of bias was assessed using the Jadad scale, a 5-item tool that assesses risk of bias due to randomization, blinding, and follow-up.¹⁹ Studies can receive a score between 0 and 5, with a higher score indicating a lower risk of bias.

Statistical analyses

The meta-analyses were conducted in Comprehensive Meta-Analysis 3.0²⁰ using a DerSimonian-Laird random-effects model²¹ to account for heterogeneity between studies. The primary outcome was the effect of saffron on total depressive symptoms in comparison with placebo control conditions. The effect of saffron on symptoms of depression as an adjunctive to medication and as a stand-alone intervention compared with medication was also computed as a secondary outcome. The effects of saffron on symptoms of anxiety compared with placebo, medication, and as an adjunctive intervention were also computed when sufficient data were available. Mean change scores in symptoms for saffron and control conditions were compared using random-effects meta-analyses to compute effect size of saffron compared with control condition as Hedges' *g* (with 95%CI). For studies that used >1 measure of the same

outcome, the measure identified as the primary outcome by the respective study was used in meta-analyses. Otherwise, an average change score across all measures was computed and used in the pooled analysis. In multi-arm trials that had >1 active saffron condition, a pooled effect was computed across all saffron arms compared with the nonsaffron comparator conditions. To examine the possibility of publication bias affecting results, Egger's *t* test was conducted. Finally, to further account for the potential impact of publication bias, a Duval and Tweedie's trim-and-fill analysis was applied to recalculate effect sizes after statistically accounting for outlier studies.

Additionally, subgroup analyses were conducted to examine the 1) effects of saffron in comparison with antidepressant medications and 2) the effect of saffron on depression when used as an adjunctive treatment alongside antidepressants (ie, studies comparing saffron to placebo in samples already taking or commencing antidepressant medications).

Heterogeneity between studies was examined using Cochran's *Q* (with *P* value) and *I*² estimates. These statistics estimate the extent to which statistical heterogeneity between studies has arisen from genuine interstudy differences rather than chance.

RESULTS

Study selection

As represented in [Figure 1](#), the search strategy resulted in 310 de-duplicated studies that were screened to identify 23 eligible studies for inclusion (see [Table 2](#)^{22–44}).

Study characteristics

A total of 1237 participants were enrolled in the included studies, with 30–128 participants in each study. Trials ran 4–12 weeks with 6 weeks being the most common trial length (*n* = 9/23). Seventeen studies investigated saffron monotherapy (*n* = 11 studies) or saffron as an adjunctive pharmacotherapy compared with placebo (*n* = 6 studies). Six studies compared saffron monotherapy with an antidepressant medication (including fluoxetine,^{23,32,40,42} imipramine,²⁵ and citalopram²⁷) No study investigated saffron as an adjunct to psychotherapy. Nineteen studies included participants with either clinical diagnosis of mental illness or clinical symptoms of mental illness using a validated tool. The average age of participants was 39 years, with a range of 14–57 years. Most studies included a mix of sexes, with 5 studies including only females and 1 study including only males. Most studies were conducted in Iran (*n* = 21/23), with 2 studies conducted in Australia.^{34,35}

Table 1 PICOS criteria for inclusion and exclusion of studies

Parameter	Criteria
Population	Human participants, both clinically diagnosed with a mental illness and otherwise
Intervention	Saffron supplementation. Both whole saffron or as an extract
Comparator	Placebo or standard antidepressant medication
Outcomes	Symptoms of mental illness, adverse events

Thirteen studies were conducted by the same research group. Risk of bias across most studies was low, with 20 studies receiving a score of 4 or 5 (out of 5) on the Jadad Scale (see [Appendix S2](#) in the Supporting Information online).

Interventions

Most studies (*n* = 19/23) used a dose of 30 mg per day of saffron. Ten studies used the stigma of saffron, 4 studies used saffron petals, 3 used crocin only, and the remaining studies used either a whole powder or did not provide further details. In 9 studies, the intervention was standardized to contain either crocin, safranal, or leptocrosalides (a measure of bioactive compounds present in saffron, including safranal and crocin isomers).

Outcome measures

Depressive symptoms (*n* = 22/23) were more commonly investigated than anxiety symptoms (*n* = 8/23). Depression and/or anxiety symptoms were measured using the Hamilton Rating Scale for Depression or Anxiety, Beck Depression Inventory, Depression Anxiety Stress Scale (DASS) 21, or Revised Child Anxiety and Depression Scale (RCADS; youth and parent versions). One study assessed mood using the Profile of Mood States (POMS) and Positive and Negative Affect Schedule (PANAS) 21 tools.

Study results

Effects of saffron on depressive symptoms. Random-effects meta-analysis found a significant and large positive effect size for saffron reducing symptoms of depression in comparison with placebo (*g* = 0.99, 95%CI = 0.61–1.37, *n* = 14 studies, *n* = 716 participants, *P* < 0.001; [Figure 2](#)^{22–27,29–31,33–40,42,44}). An additional study that could not be entered into the meta-analysis due to insufficient available data also found that saffron significantly improved depressive symptoms compared with placebo (*P* < 0.0001).⁴³ There was significant heterogeneity across the study data (*Q* =

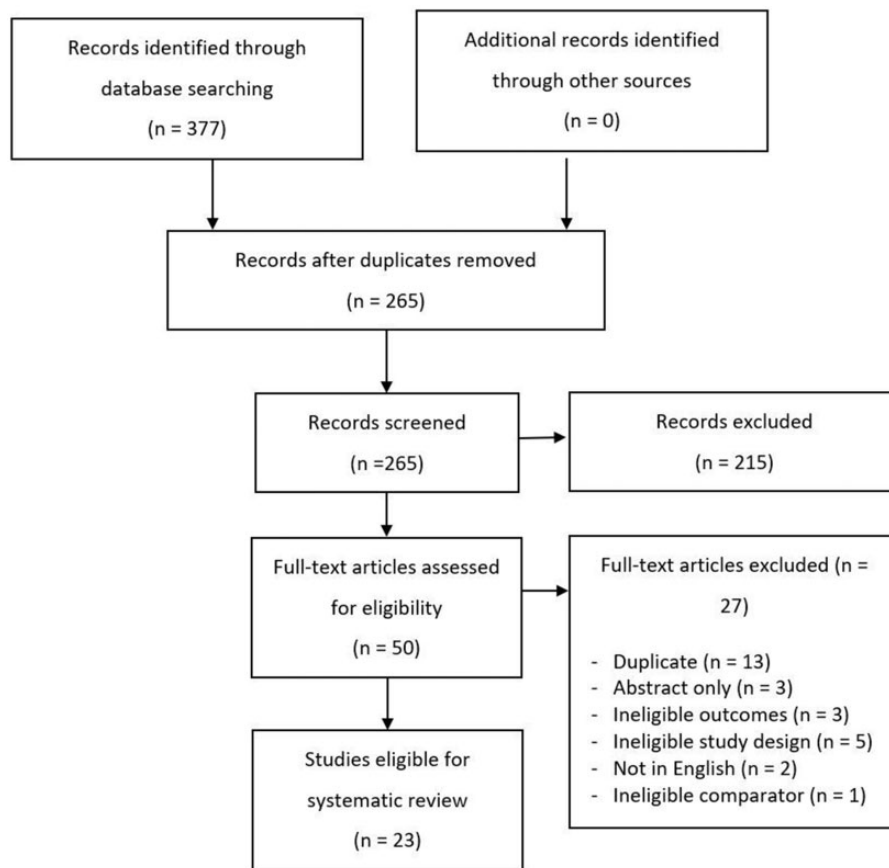


Figure 1 Flow diagram of the literature search process.

71.8, $P < 0.001$, $I^2=81.9\%$). Egger's regression test found strong evidence of publication bias (Intercept = 6.99, $P = 0.007$). The funnel plot of publication bias is displayed in [Appendix S3](#) in the Supporting Information online. Correcting for publication bias using a trim-and-fill analysis increased the effect size of saffron supplementation ($g = 1.14$, 95%CI = 0.74–1.52).

When compared with antidepressant medications, there was no significant difference between saffron and medications ($g = -0.17$, 95%CI = 0.50–0.17, $n = 5$ studies, $n = 210$ participants, $P = 0.33$; [Figure 2](#)^{22–27,29–31,33–40,42,44}). There was a low degree of heterogeneity across the study data ($Q = 6.16$, $P = 0.19$, $I^2 = 35.1\%$). One study for which sufficient information was not provided to be included in the meta-analysis also found no significant difference in depressive symptoms between saffron and medication ($P = 0.61$).³²

Meta-analysis of studies that investigated the effect of saffron as an adjunct to pharmacotherapy (ie, in studies comparing saffron to placebo in people taking antidepressants) reported a large significant benefit from saffron supplementation ($n = 4$ trials, $n = 144$ participants, $g = 1.23$, 95%CI = 0.13–2.33, $P = 0.028$, $Q = 27.62$, $I^2 = 89.1\%$). One study that could not be included in the meta-analysis reported no significant

difference in depressive symptoms between the adjunctive group (fluoxetine and saffron) and control (fluoxetine and placebo) ($P = 0.560$).⁴¹

Effects of saffron on symptoms of anxiety. [Figure 3](#)^{28,34–37,44,28,34–37,44} displays the effects of saffron monotherapy and adjunctive therapy on symptoms of anxiety across 6 RCTs compared with placebo ($n = 375$ participants). Random-effects meta-analysis found a large positive effect size for saffron on reducing symptoms of anxiety in comparison with placebo control conditions ($g = 0.95$, 95%CI = 0.27–1.63, $P < 0.006$). There was significant heterogeneity across the study data ($Q = 44.38$, $P < 0.001$, $I^2 = 88.74\%$). Egger's regression test found strong evidence of publication bias (Intercept = 0.12, $P = 0.028$). Correcting for publication bias using a trim-and-fill analysis increased the effect size of saffron supplementation ($g = 1.40$, 95%CI = 0.60–2.150). There were insufficient studies to conduct a meta-analysis of the effect of saffron on anxiety in comparison with antidepressant medications or to conduct subgroup analysis of saffron as an adjunctive treatment. One study that investigated the effect of saffron for anxiety symptoms compared with citalopram found

Table 2 Summary table of included studies

Reference	Study details	Population details	Intervention, mg/d	Outcomes ^a	Results
Abedimaneh et al (2017) ²²	<p>Study design: Randomized, double-blind, placebo-controlled</p> <p>Country: Iran</p> <p>Sample size (n): 63 enrolled, 58 completed</p> <p>Total study period: 8 wk</p>	<p>Male and female coronary artery disease (CAD) patients</p> <p>Age in years (average): 55</p>	<p>30 mg saffron aqueous extract (SAE; stigma)</p> <p>OR 30 mg crocin (stigma)</p> <p>OR placebo</p>	<p>Outcomes measured: Depression measured using BDI-II</p> <p>Outcomes measured at: Baseline and after 8 wk of intervention</p>	<p>The BDI-II score significantly decreased in the SAE and crocin groups compared with -placebo from baseline to endpoint ($P < 0.001$). No significant difference between the crocin and SAE groups in total BDI-II score at endpoint ($P = 0.999$)</p>
Akhondzadeh Basti et al (2007) ²³	<p>Study design: Randomized, double-blind, parallel group</p> <p>Country: Iran</p> <p>Sample size: 40 enrolled, 38 completed</p> <p>Total study period: 8 wk</p>	<p>Male and female outpatients who met DSM-IV criteria for major depression based on the SCID-IV</p> <p>Age in years (average): 34</p>	<p>30 mg saffron (petal) OR 20 mg fluoxetine</p>	<p>Outcomes measured: Depression measured using HAM-D-17</p> <p>Outcomes measured at: Baseline, wk 1, wk 2, wk 4, wk 6, and wk 8 (endpoint)</p>	<p>The HAM-D-17 score significantly decreased in both the saffron and fluoxetine groups from baseline to endpoint ($P < 0.001$). No significant difference at endpoint between the 1 groups ($P = 0.84$)</p>
Akhondzadeh et al (2005) ²⁴	<p>Study design: Randomized, double-blind, parallel group</p> <p>Country: Iran</p> <p>Sample size: 40 enrolled, 35 completed</p> <p>Total study period: 6 wk</p>	<p>Male and female outpatients who met DSM-IV criteria for major depression based on the SCID-IV</p> <p>Age in years (average): 36</p>	<p>30 mg saffron (stigma) OR placebo</p>	<p>Outcomes measured: Depression measured using HAM-D-17</p> <p>Outcomes measured at: Baseline, wk 1, wk 2, wk 4, and wk 6 (endpoint)</p>	<p>The HAM-D-17 score significantly decreased in both the saffron and placebo groups from baseline to endpoint ($P < 0.001$). However, the saffron group had significantly lower HAM-D-17 scores at endpoint compared with placebo ($P < 0.001$)</p>
Akhondzadeh et al (2004) ²⁵	<p>Study design: Randomized, double-blind, parallel group</p> <p>Country: Iran</p> <p>Sample size: 30 enrolled, 30 completed</p> <p>Total study period: 6 wk</p>	<p>Male and female outpatients who met DSM-IV criteria for major depression based on the SCID-IV</p> <p>Age in years (average): 34</p>	<p>30 mg saffron (stigma) OR 100 mg imipramine</p>	<p>Outcomes measured: Depression measured using HAM-D-17</p> <p>Outcomes measured at: Baseline, wk 1, wk 2, wk 3, wk 4, wk 5, and wk 6 (endpoint)</p>	<p>The HAM-D-17 score significantly decreased in both the saffron and imipramine groups from baseline to endpoint ($P < 0.001$). No significant difference at endpoint between the 2 groups ($P = 0.09$)</p>

(continued)

Table 2 Continued

Reference	Study details	Population details	Intervention, mg/d	Outcomes ^a	Results
Agha-Hosseini et al (2008) ²⁶	<p>Study design: Randomized, double-blind, placebo-controlled</p> <p>Country: Iran</p> <p>Sample size: 50 enrolled, 47 completed</p> <p>Total study period: 8 wk; or 2 menstrual cycles (cycles 3 and 4)</p>	<p>Women with regular menstrual cycles and experience of PMS symptoms for at least 6 mo</p> <p>Age in years (average): 34</p>	<p>30 mg saffron (petal) OR placebo</p>	<p>Outcomes measured: Depression measured using HAM-D-17 PMS factors, including mood (eg, anxiety, irritability, depression, nervous tension, mood swings, and out of control), measured using Daily Symptom Report Checklist</p> <p>Outcomes measured at: Baseline (ie, at the end of cycle 2, a premenstrual stage—as close as possible to 2 d prior to the onset of menstruation), and the premenstrual stage of cycles 3 and 4.</p> <p>Outcomes measured: Depression measured using HAM-D-17 Anxiety measured using HAM-A</p> <p>Outcomes measured at: Baseline, wk 2, wk 4, and wk 6 (endpoint)</p>	<p>The HAM-D-17 score significantly decreased in the saffron group compared with placebo from baseline to endpoint ($P < 0.001$). The total Daily Symptom Report Checklist score significantly decreased in the saffron group compared with placebo from baseline to endpoint, ($P = 0.002$)</p>
Ghajar et al (2017) ²⁷	<p>Study design: Randomized, double-blind, parallel group</p> <p>Country: Iran</p> <p>Sample size: 66 enrolled, 60 completed</p> <p>Total study period: 6 wk</p>	<p>Male and female patients who met DSM-IV criteria for mild-to-moderate major depression coupled with anxious distress</p> <p>Age in years (average): 36</p>	<p>30 mg saffron (stigma) OR 40 mg citalopram</p>	<p>Outcomes measured: Depression measured using HAM-D-17 Anxiety measured using HAM-A</p> <p>Outcomes measured at: Baseline, wk 2, wk 4, and wk 6 (endpoint)</p>	<p>The HAM-D-17 and HAM-A scores significantly decreased in both the saffron and citalopram groups from baseline to endpoint ($P < 0.001$). No significant difference for either HAM-D-17 or HAM-A scores at endpoint between the 2 groups ($P = 0.715$ and $P = 0.999$, respectively).</p>
Jafarnia et al (2017) ²⁸	<p>Study design: Randomized, double-blind, placebo-controlled</p> <p>Country: Iran</p> <p>Sample size: 40 enrolled, 40 completed</p> <p>Total study period: 6 wk</p>	<p>Male and female patients who met DSM-IV criteria for mild-to-moderate generalized anxiety disorder (GAD) and were receiving sertraline</p> <p>Age in years (average): 31</p>	<p>500 mg capsule containing 450 mg Saffron (type not recorded) AND 50 mg sertraline OR placebo AND 50 mg sertraline</p>	<p>Outcomes measured: Anxiety measured using HAM-A</p> <p>Outcomes measured at: Baseline, wk 3, and wk 6 (endpoint)</p>	<p>The HAM-A score significantly decreased in both the saffron (coupled with sertraline) and placebo (coupled with Sertraline) groups from baseline to endpoint ($P < 0.000$). However, the saffron (coupled with sertraline) group had significantly lower HAM-A scores at endpoint compared with placebo (coupled with sertraline) ($P < 0.005$)</p>

(continued)

Table 2 Continued

Reference	Study details	Population details	Intervention, mg/d	Outcomes ^a	Results
Jam et al (2017) ²⁹	<p>Study design: Randomized, double-blind, placebo-controlled</p> <p>Country: Iran</p> <p>Sample size: 34 enrolled, 33 completed</p> <p>Total study period: 8 wk</p>	<p>Male and female patients with metabolic syndrome (MetS) and depressive symptoms based on the BDI</p> <p>Age in years (average): 46</p>	30 mg saffron (crocin) OR placebo	<p>Outcomes measured: Depression measured using BDI</p> <p>Outcomes measured at: Baseline and week 8 (endpoint)</p>	<p>The BDI score significantly decreased in the saffron group but not in the placebo group from baseline to endpoint ($P < 0.005$ and $P > 0.05$, respectively). Significant difference at endpoint between the 2 groups ($P = 0.013$)</p> <p>The BDI score significantly decreased in both the saffron (coupled with fluoxetine) and placebo (coupled with fluoxetine) groups from baseline to endpoint ($P < 0.05$). No significant difference at endpoint between the 2 groups ($P < 0.056$)</p>
Jelodar et al (2018) ³⁰	<p>Study design: Randomized, double-blind, placebo-controlled</p> <p>Country: Iran</p> <p>Sample size: 40 enrolled, 40 completed</p> <p>Total study period: 4 wk</p>	<p>Male and female outpatients who met DSM-IV criteria for major depression based on the SCID-IV</p> <p>Age in years (range): 20–55</p>	30 mg saffron (stigma) AND 20 mg fluoxetine OR placebo AND 20 mg fluoxetine	<p>Outcomes measured: Depression measured using BDI</p> <p>Outcomes measured at: Baseline and week 4 (endpoint)</p>	<p>The HDRS score significantly decreased in both saffron and placebo groups from baseline to endpoint ($P < 0.01$). However, the saffron group had significantly lower HDRS scores at endpoint compared with placebo ($P < 0.001$)</p> <p>^aSignificance of reduction in HDRS score within groups for saffron and fluoxetine from baseline to endpoint not recorded.</p> <p>No significant difference at endpoint between the 2 groups ($P = 0.37$)</p> <p>^aSignificance of reduction in HDRS score within groups for saffron (coupled with fluoxetine) and placebo (coupled with fluoxetine) from baseline to endpoint not recorded.</p> <p>No significant difference at endpoint between the 2 groups ($P = 0.278$)</p>
Kashani et al (2018) ³¹	<p>Study design: Randomized, double-blind, placebo-controlled</p> <p>Country: Iran</p> <p>Sample size: 60 enrolled, 56 completed</p> <p>Total study period: 6 wk</p>	<p>Women who met DSM-IV criteria for major depression and mild-to-moderate depression based on HDRS as well as postmenopausal hot flashes</p> <p>Age in years (average): 55</p>	30 mg Saffron (stigma) OR Placebo	<p>Outcomes measured: Depression measured using HDRS</p> <p>Outcomes measured at: Baseline, wk 2, wk 4, and wk 6 (endpoint)</p>	<p>The HDRS score significantly decreased in both saffron and placebo groups from baseline to endpoint ($P < 0.01$). However, the saffron group had significantly lower HDRS scores at endpoint compared with placebo ($P < 0.001$)</p> <p>^aSignificance of reduction in HDRS score within groups for saffron and fluoxetine from baseline to endpoint not recorded.</p> <p>No significant difference at endpoint between the 2 groups ($P = 0.37$)</p> <p>^aSignificance of reduction in HDRS score within groups for saffron (coupled with fluoxetine) and placebo (coupled with fluoxetine) from baseline to endpoint not recorded.</p> <p>No significant difference at endpoint between the 2 groups ($P = 0.278$)</p>
Kashani et al (2017) ³²	<p>Study design: Randomized, double-blind, parallel group</p> <p>Country: Iran</p> <p>Sample size: 68 enrolled, 64 completed</p> <p>Total study period: 6 wk</p>	<p>Women who met DSM-IV criteria for postpartum depression 4–12 wk after childbirth as well as scoring >10 and <18 on HDRS</p> <p>Age in years (average): 30</p>	30 mg saffron (stigma) OR 20 mg fluoxetine	<p>Outcomes measured: Depression measured using HDRS</p> <p>Outcomes measured at: Baseline, wk 1, wk 3, and wk 6 (endpoint)</p>	<p>The HDRS score significantly decreased in both saffron and placebo groups from baseline to endpoint ($P < 0.01$). However, the saffron group had significantly lower HDRS scores at endpoint compared with placebo ($P < 0.001$)</p> <p>^aSignificance of reduction in HDRS score within groups for saffron and fluoxetine from baseline to endpoint not recorded.</p> <p>No significant difference at endpoint between the 2 groups ($P = 0.37$)</p> <p>^aSignificance of reduction in HDRS score within groups for saffron (coupled with fluoxetine) and placebo (coupled with fluoxetine) from baseline to endpoint not recorded.</p> <p>No significant difference at endpoint between the 2 groups ($P = 0.278$)</p>
Kashani et al (2013) ³³	<p>Study design: Randomized, double-blind, placebo-controlled</p> <p>Country: Iran</p> <p>Sample size: 38 enrolled, 34 completed</p> <p>Total study period: 4 wk</p>	<p>Female outpatients who met DSM-IV criteria for major depression; were being treated with 40 mg/d of fluoxetine for at least 6 wk prior to entry; and, whose depressive symptoms had been stabilized (ie, 50% reduction in depression score)</p> <p>Age in years (average): 35</p>	30 mg saffron (petal) AND 40 mg fluoxetine OR placebo AND 40 mg fluoxetine	<p>Outcomes measured: Depression measured using HDRS</p> <p>Outcomes measured at: Baseline, wk 2, and wk 4 (endpoint)</p>	<p>The HDRS score significantly decreased in the saffron group but not in the placebo group from baseline to endpoint ($P < 0.005$ and $P > 0.05$, respectively). Significant difference at endpoint between the 2 groups ($P = 0.013$)</p> <p>The BDI score significantly decreased in both the saffron (coupled with fluoxetine) and placebo (coupled with fluoxetine) groups from baseline to endpoint ($P < 0.05$). No significant difference at endpoint between the 2 groups ($P < 0.056$)</p> <p>The HDRS score significantly decreased in both saffron and placebo groups from baseline to endpoint ($P < 0.01$). However, the saffron group had significantly lower HDRS scores at endpoint compared with placebo ($P < 0.001$)</p> <p>^aSignificance of reduction in HDRS score within groups for saffron and fluoxetine from baseline to endpoint not recorded.</p> <p>No significant difference at endpoint between the 2 groups ($P = 0.37$)</p> <p>^aSignificance of reduction in HDRS score within groups for saffron (coupled with fluoxetine) and placebo (coupled with fluoxetine) from baseline to endpoint not recorded.</p> <p>No significant difference at endpoint between the 2 groups ($P = 0.278$)</p>

(continued)

Table 2 Continued

Reference	Study details	Population details	Intervention, mg/d	Outcomes ^a	Results
Kell et al (2017) ^{3,4}	<p>Study design: Randomized, double-blind, parallel group, placebo-controlled</p> <p>Country: Australia</p> <p>Sample size: 128 enrolled, 121 completed</p> <p>Total study period: 4 wk</p>	<p>Male and females self-reporting low mood but not diagnosed with depression or another mood disorder and who were otherwise healthy</p> <p>Age in years (average): 39</p>	28 mg saffron (stigma) OR saffron 22 mg (stigma) saffron OR placebo	<p>Outcomes measured:</p> <p>Mood measured using Profile of Mood State (POMS) and Positive and Negative Affect Schedule (PANAS-21)</p> <p>Depression, anxiety and stress measured using the Depression, Anxiety and Stress Scale (DASS-21)</p> <p>Outcomes measured at: Baseline and wk 4 (endpoint)</p>	<p>The POMS Total Mood Disturbance score significantly decreased for the 28-mg saffron group compared with Placebo at endpoint ($P < 0.001$). No treatment effect on the POMS Total Mood Disturbance score for the 22-mg saffron group.</p> <p>The PANAS-21 score for Positive Affect showed no significant difference at endpoint among the 3 groups ($P = 0.124$). However, the PANAS-21 score for Negative Affect significantly decreased for the 28-mg saffron group compared with placebo at endpoint ($P < 0.001$).</p> <p>The DASS-21 score for depression decreased significantly more for the 28-mg saffron group compared with both the 22-mg saffron and placebo groups at endpoint ($P < 0.001$ and $P = 0.001$, respectively). No significant difference at endpoint between the 22-mg saffron and placebo groups ($P = 0.449$).</p> <p>The DASS-21 score for anxiety significantly decreased for the 28-mg saffron group compared with placebo at endpoint ($P < 0.010$). No significant difference between the 22-mg saffron group compared with the 28-mg saffron or placebo groups at endpoint ($P = 0.149$ and $P = 0.625$, respectively).</p>

(continued)

Table 2 Continued

Reference	Study details	Population details	Intervention, mg/d	Outcomes ^a	Results
Lopresti et al (2018) ³⁵	<p>Study design: Randomized, double-blind, placebo-controlled</p> <p>Country: Australia</p> <p>Sample size: 80 enrolled, 68 completed</p> <p>Total study period: 8 wk</p>	<p>Male and female youth who were assessed as suffering from mild-to-moderate anxiety and depressive symptoms</p> <p>Age in years (average): 14</p>	14 mg saffron (stigma) OR placebo	<p>Outcomes measured: Depression and anxiety measured using youth and parent reports for Revised Child Anxiety and Depression Scale (RCADS)</p> <p>Subscales: separation anxiety; generalized anxiety; panic; social phobia; obsessions/compulsions; depression</p> <p>Outcomes measured at: Baseline, wk 2, wk 4, wk 6, and wk 8 (endpoint)</p>	<p>The DASS-21 score for stress significantly decreased for the 28-mg saffron group compared with both the 22-mg saffron and placebo groups at endpoint ($P < 0.001$ and $P = 0.001$, respectively)</p> <p>Youth reports: The total RCADS score significantly decreased from baseline to endpoint for the saffron group compared with placebo ($P < 0.049$), as did 3 subscale scores: separation anxiety ($P = 0.003$); social phobia ($P = 0.023$); and depression ($P = 0.016$).</p> <p>Parent reports: No significant difference from baseline to endpoint for total RCADS scores between groups ($P = 0.749$). Saffron had a significant mean improvement ($P = 0.026$), and in 2 subscales from baseline to endpoint: generalized anxiety ($P < 0.01$); and, obsessions/compulsions ($P < 0.01$)</p>
Mazidi et al (2016) ³⁶	<p>Study design: Randomized, double-blind, placebo-controlled</p> <p>Country: Iran</p> <p>Sample size: 60 enrolled, 54 completed</p> <p>Total study period: 12 wk</p>	<p>Male and female patients who met DSM-IV criteria for mild-to-moderate mixed anxiety and depression based on the SCID-IV</p> <p>Age in years (average): 43</p>	100 mg saffron (stigma) OR placebo	<p>Outcomes measured: Depression measured using BDI</p> <p>Anxiety measured using BAI</p> <p>Outcomes measured at: Baseline, wk 3, wk 6, and wk 12 (endpoint)</p>	<p>The BDI and BAI scores significantly decreased in the saffron group compared with placebo from baseline to endpoint ($P < 0.001$)</p>
Moazen-Zadeh et al (2018) ³⁷	<p>Study design: Randomized, double-blind, placebo-controlled</p> <p>Country: Iran</p> <p>Sample size: 76 enrolled, 37 completed</p> <p>Total study period: 12 wk</p>	<p>Male and female patients referred for on-pump coronary artery bypass grafting surgery with Wechsler Memory Scale-Revised (WMS-R) score >70 and aged <70 y.</p> <p>Enrolled to receive saffron or placebo from 2 d before surgery up to 12 wk after.</p> <p>Age in years (average): 57</p>	30 mg saffron (stigma) OR placebo	<p>Outcomes measured: Anxiety and Depression measured using Hospital Anxiety and Depression Scale (HADS)</p> <p>Outcomes measured at: Baseline and wk 12 (endpoint)</p>	<p>No significant difference from baseline to endpoint for HADS anxiety and/or depression subscale scores between saffron and placebo groups ($P = 0.619$ and $P = 0.208$, respectively)</p>

(continued)

Table 2 Continued

Reference	Study details	Population details	Intervention, mg/d	Outcomes ^a	Results
Modabbernia et al (2012) ³⁸	<p>Study design: Randomized, double-blind, placebo-controlled</p> <p>Country: Iran</p> <p>Sample size: 36 enrolled, 30 completed</p> <p>Total study period: 4 wk</p>	<p>Male patients who met DSM-IV criteria for major depressive disorder (MDD) and were currently being treated with fluoxetine (40 mg / day for a minimum of 6 wk prior to entry)</p> <p>Age in years (average): 38</p> <p>Male and female outpatients who met DSM-IV criteria for major depression based on the SCID-IV, but were free of all psychiatric medication for at least 4 wk prior to entry</p> <p>Age in years (average): 35</p>	<p>30 mg saffron (stigma) AND 40 mg fluoxetine OR placebo AND 40 mg fluoxetine</p>	<p>Outcomes measured: Depression measured using HDRS</p> <p>Outcomes measured at: Baseline and wk 4 (endpoint)</p>	<p>No significant difference from baseline to endpoint for HDRS scores between saffron (coupled with fluoxetine) and placebo (coupled with fluoxetine) groups ($P = 0.178$)</p>
Moshiri et al (2006) ³⁹	<p>Study design: Randomized, double-blind, placebo-controlled</p> <p>Country: Iran</p> <p>Sample size: 40 enrolled, 36 completed</p> <p>Total study period: 6 wk</p>	<p>Male and female outpatients who met DSM-IV criteria for mild-to-moderate depression based on the SCID-IV</p> <p>Age in years (average): 36</p>	<p>30 mg saffron (petal) OR placebo</p>	<p>Outcomes measured: Depression measured using HAM-D-17</p> <p>Outcomes measured at: Baseline, wk 1, wk 2, wk 4, and wk 6 (endpoint)</p>	<p>The HAM-D-17 score significantly decreased in both the saffron and placebo groups from baseline to endpoint ($P < 0.001$). However, the saffron group had significantly lower HAM-D-17 scores at endpoint compared with placebo ($P < 0.001$)</p>
Noorbala et al (2005) ⁴⁰	<p>Study design: Randomized, double-blind, parallel group</p> <p>Country: Iran</p> <p>Sample size: 40 enrolled, 38 completed</p> <p>Total study period: 6 wk</p>	<p>Male and female outpatients who met DSM-IV criteria for mild-to-moderate depression based on the SCID-IV</p> <p>Age in years (average): 36</p>	<p>30 mg saffron (stigma) OR 20 mg fluoxetine</p>	<p>Outcomes measured: Depression measured using HAM-D-17</p> <p>Outcomes measured at: Baseline, wk 1, wk 2, wk 4, and wk 6 (endpoint)</p>	<p>The HAM-D-17 score significantly decreased in both the saffron and fluoxetine groups from baseline to endpoint ($P < 0.001$). No significant difference at endpoint between the 2 groups ($P = 0.71$)</p>
Sahraian et al (2016) ⁴¹	<p>Study design: Randomized, double-blind, placebo-controlled</p> <p>Country: Iran</p> <p>Sample size: 40 enrolled, 30 completed</p> <p>Total study period: 4 wk</p>	<p>Male and female outpatients who met DSM-IV criteria for major depression based on the SCID-IV</p> <p>Age in years (average): 43</p>	<p>30 mg saffron (type not recorded) AND 20 mg fluoxetine OR placebo AND 20 mg fluoxetine</p>	<p>Outcomes measured: Depression measured using BDI</p> <p>Outcomes measured at: Baseline and week 4 (endpoint)</p>	<p>The BDI score significantly decreased in both the saffron (coupled with fluoxetine) and placebo (coupled with fluoxetine) groups from baseline to endpoint ($P < 0.003$ and $P < 0.000$, respectively). No significant difference at endpoint between the 2 groups ($P = 0.560$)</p>
Shahmansouri et al (2014) ⁴²	<p>Study design: Randomized, double-blind, parallel group</p> <p>Country: Iran</p> <p>Sample size: 44 enrolled, 40 completed</p>	<p>Male and female outpatients who met DSM-IV criteria for mild-to-moderate depression based on the SCID-IV and HDRS scores of 14–22. Participants had also</p>	<p>30 mg saffron (stigma) OR 40 mg fluoxetine</p>	<p>Outcomes measured: Depression measured using HDRS</p> <p>Outcomes measured at: Baseline, wk 3, and wk 6 (endpoint)</p>	<p>The HDRS score significantly decreased in both the saffron and fluoxetine groups from baseline to endpoint. No significant difference at</p>

(continued)

Table 2 Continued

Reference	Study details	Population details	Intervention, mg/d	Outcomes ^a	Results
Tabeshpour et al (2017) ⁴³	Total study period: 6 wk Study design: Randomized, double-blind, placebo-controlled Country: Iran Sample size: 78 enrolled, 60 completed Total study period: 8 wk	undergone percutaneous coronary intervention in the last 6 mo Age in years (average): 53 Breastfeeding mothers with mild-to-moderated depression based on "clinical interviews" Age in years (average): 36	30 mg saffron (stigma) OR placebo	Outcomes measured: Depression measured using BDI-II Outcomes measured at: Baseline, wk 4, and wk 8 (endpoint)	endpoint between the 2 groups ($P = 0.70$) The BDI score significantly decreased in both the saffron and placebo groups from baseline to endpoint ($P < 0.003$ and $P < 0.01$, respectively). However, the saffron group had significantly lower BDI scores at endpoint compared with placebo ($P < 0.001$)
Talaei et al (2015) ⁴⁴	Study design: Randomized, double-blind, placebo-controlled Country: Iran Sample size: 46 enrolled, 40 completed Total study period: 4 wk	Male and female outpatients who met DSM-IV criteria for major depression based on the SCID-IV Age in years (average): 36	30 mg saffron (crocin) AND 20 mg fluoxetine; OR 50 mg sertraline; OR 20 mg citalopram -OR- placebo AND 20 mg fluoxetine; OR 50 mg sertraline; OR 20 mg citalopram	Outcomes measured: Depression measured using BDI Anxiety measured using BAI Bipolar disorder measured using Mood Disorder Questionnaire (MDQ) Outcomes measured at: Baseline and wk 4 (endpoint)	The BDI and BAI scores significantly decreased in both groups from baseline to endpoint ($P < 0.0001$). However, the saffron group had significantly lower BDI and BAI scores at endpoint compared with placebo ($P < 0.0001$). ^a Data for MDQ not reported

Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CAD, coronary artery disease; DASS-21, Depression Anxiety Stress Scales; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; GAD, generalized anxiety disorder; HADS, Hospital Anxiety and Depression Scale; HAM-A, Hamilton Anxiety Rating Scale; HAM-D-17, Hamilton Depression Rating Scale; HDRS, Hamilton Rating Scale for Depression; MDD, major depressive disorder; MetS, metabolic syndrome; PANAS-21, Positive and Negative Affect Schedule; PMS, premenstrual syndrome; POIMS, Profile Of Mood States; RCADS, Revised Children's Anxiety and Depression Scale; RVAD: Revised Child Anxiety and Depression Scale; SAE, serious adverse event; SCID-IV, Structured Clinical Interview for DSM-5; WMS-R, Wechsler Memory Scale.

^aOnly outcomes of interest (eg, depression and anxiety symptoms) were extracted and are presented.

no significant difference between treatment groups ($P < 0.001$).²⁷

Sensitivity analyses. Sensitivity analyses were performed to exclude 1 outlier study that could be influencing the overall findings.⁴⁴ Exclusion of this study only slightly reduced the overall effect size of saffron on depressive symptoms compared with placebo ($g = 0.84$, 95%CI = 0.53–1.16, $P < 0.001$), although large heterogeneity ($Q = 45.45$, $P < 0.001$, $I^2=73.8\%$) and significant publication bias was still evident in the remaining 13 studies (Egger's regression intercept = 4.957, $P = 0.043$).

When performing sensitivity analyses with the outlier study excluded for anxiety outcomes, the effects of saffron compared with placebo were reduced substantially, although overall results remained the same ($g = 0.48$, 95%CI = 0.25–0.70, $P < 0.001$). There was also little indication of heterogeneity ($Q = 3.39$, $P = 0.50$, $I^2=0\%$) or publication bias (Egger's regression intercept = 0.23, $P = 0.47$) in the remaining 5 studies, although this is likely due to standard tests for detecting heterogeneity/publication bias in meta-analysis being underpowered in this small number of studies.

Effects of saffron on additional outcomes. One study found a significant improvement in total score of mood disturbances ($P < 0.001$) and subscales of fatigue ($P = 0.007$), tension ($P = 0.025$), vigor ($P = 0.007$), confusion ($P = 0.001$), negative affect ($P = 0.001$), and stress ($P < 0.001$) when saffron supplementation was compared with placebo.³⁴ Another study found significant improvements in self-reported measures of internalizing symptoms ($P = 0.049$), separation anxiety ($P = 0.003$), and social phobia ($P = 0.023$) compared with placebo.³⁵ General mental health was improved in 1 study compared with placebo ($P < 0.001$),⁴⁴ and the emotional functioning subscale of a quality-of-life questionnaire also improved in a separate study after saffron supplementation compared with placebo ($P < 0.001$).²²

Adverse events

Adverse events were reported for most studies ($n = 21/23$). Headache, nausea, anxiety, constipation, dry mouth, and appetite changes were the most commonly reported symptoms in both arms. No study found symptoms to occur in the saffron group at a statistically higher rate than in the placebo and medication groups.

DISCUSSION

This is the most comprehensive meta-analysis to evaluate the effects of saffron supplementation for depressive and anxiety symptoms. The inclusion of adult,

adolescent, and subclinical depressive and anxiety populations, as well as the examination of both depression and anxiety outcomes, provides a greater understanding of the possible efficacy of saffron as an intervention across the common mental disorders.

The results of this meta-analysis are consistent with 2 prior meta-analyses that investigated saffron for mild-to-major depression only.^{16,17} Saffron had a significant large positive effect size when compared with placebo for both depression ($g = 0.99$, $P < 0.001$) and anxiety ($g = 0.95$, $P < 0.006$) outcomes. For depressive outcomes, saffron also had a significant large positive effect size when used as an adjunctive treatment to antidepressants ($g = 1.23$, $P = 0.028$), and when compared with antidepressant medications, there was no significant difference between groups ($g = -0.17$, $P = 0.33$). The included studies demonstrate that saffron supplementation appears to be well-tolerated with few adverse events being reported by the included studies or by other authors.⁴⁵ However, all studies to date have been of relatively short duration and with a limited sample size. Therefore, longer-term trials that are suitably powered are required to assess the safety of saffron supplementation.

In the context of standard interventions for depression and anxiety, the results from the placebo-controlled trials suggest an effect size that is considerably greater than standard pharmacotherapy, such as selective serotonin reuptake inhibitors (Cohen's $d = 0.30$).⁴⁶ However, the 5 trials directly comparing saffron with antidepressant medication found no statistically significant difference ($P = 0.33$). Due to the large effect sizes, the publication bias detected for both outcomes, and the majority of trials being conducted in 1 region, many by the same research group ($n = 13/23$), there is a need to replicate these results within other populations and in large, well-powered, rigorous trials before clinical recommendations are justified. Similarly, greater rigor regarding good manufacturing practice and standardization, dosage, and characterization of the active ingredients is needed.

In addition to the need to replicate existing studies, additional areas are recommended for future studies. First, the use of saffron for other mental illnesses is currently underexplored. Whereas 7 studies assessed anxiety symptoms, only 1 study included participants with a diagnosed anxiety disorder. Similarly, 1 study evaluated the safety and feasibility of saffron in schizophrenia, but no efficacy trials have been conducted to date.⁴⁷ Furthermore, there is a need to explore comparative efficacy of the different components of saffron. One study found that saffron petal and stigma had equivalent efficacy in treating depressive symptoms in participants with major depression, but there is insufficient

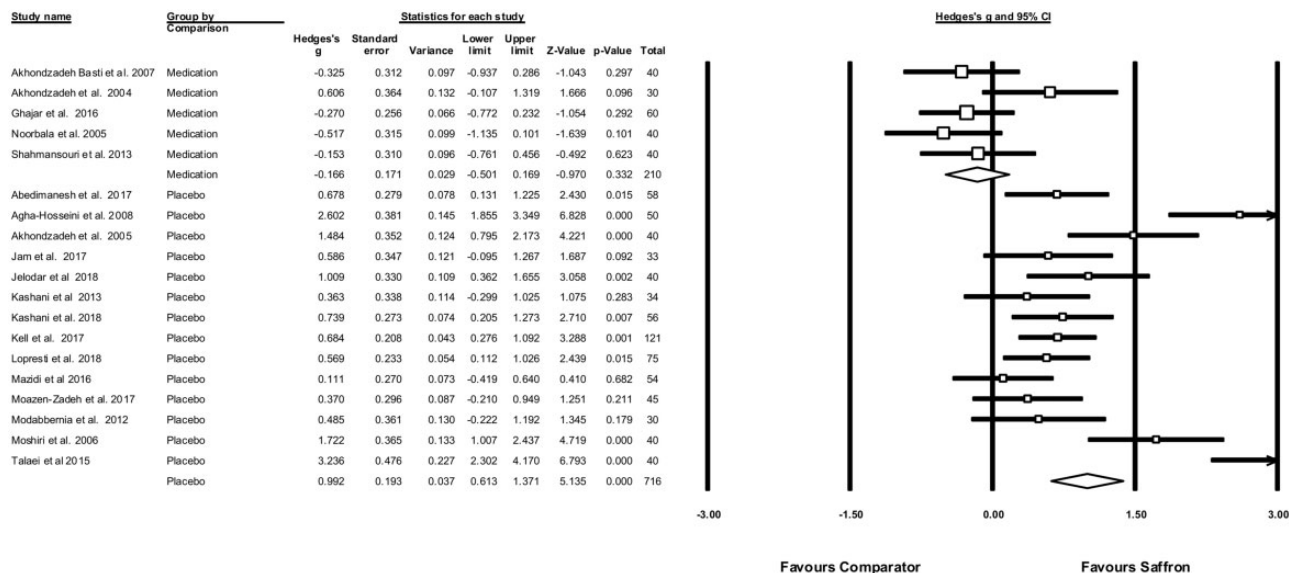


Figure 2 Meta-analysis showing effects of saffron on symptoms of depression in a) comparison with antidepressant medications, and b) comparison with placebo controls. Box size represents study weighting. Diamond represents overall effect size and 95% confidence intervals.

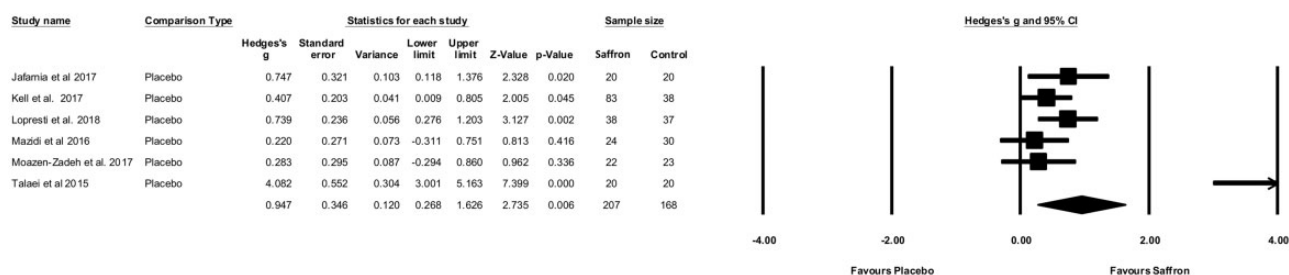


Figure 3 Meta-analysis of the effects of saffron on symptoms of anxiety. Box size represents study weighting. Diamond represents overall effect size and 95% confidence intervals.

literature to comment on particular components at this stage.²³ Because of the high cost of saffron for culinary use, previous reviews have recommended the investigation of the efficacy of less expensive parts of saffron (eg, petal and corm).⁴ However, because of the small therapeutic dosage used in current studies, the cost of saffron formulations is unlikely to be considerably higher than for other nutraceutical interventions.

Preclinical studies suggest that compounds contained within saffron have a range of potentially relevant mechanisms of action, including antioxidant and anti-inflammatory properties, and are able to modulate BDNF expression and the HPA axis.⁴ However, these pathways have been largely unexplored within clinical trials. Hence, there is a need to measure markers of relevant pathways within future clinical trials to explore the association between changes in these biological markers and clinical symptoms. Furthermore, as demonstrated by Rapaport et al,⁴⁸ who reported that treatment response to n-3 (eicosapentaenoic acid) was greater in those with higher inflammation at baseline, measuring

relevant biomarkers may provide valuable information regarding specific populations and participant stratification to determine who is likely to respond to saffron treatment. Related to this is the need for dose-finding studies to establish the optimal dosing regimen. Most studies have used 30 mg of saffron per day; however, it is unclear whether there are other regimens that may improve the therapeutic effect.

CONCLUSION

In summary, the existing evidence suggests a potential for saffron to be an efficacious intervention for symptoms of depression and anxiety. However, the strength of this conclusion is moderated by the lack of large-scale trials and risk of publication bias among the many small-scale pilot trials published on this topic. Indeed, the large effect sizes reported for some studies require replication in further clinical trials that address methodological limitations and the lack of regional diversity before clinical recommendations can be made. Trials that

explore the mechanisms of action of saffron, dosage, active ingredients, long-term safety, and the efficacy in diagnosed mental illnesses are also required.

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Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Appendix S1 PRISMA checklist

Appendix S2 Risk-of-bias summaries for included studies

Appendix S3 Forest-plot of publication bias

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