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

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

Published in:
Nutrition Reviews

DOI:
10.1093/nutrit/nuz023

Licence:
Other

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

Article type: Special article

Wolfgang Marx[1]*, Melissa Lane[1], Tetyana Rocks[1], Anu Ruusunen[1,2,3], Amy Loughman[1], Adrian Lopresti[4], Skye Marshall[5], Michael Berk[6,7], Felice Jacka[1,8,9^], Olivia M. Dean[6,10,11^]

*Corresponding author: wolf.marx@deakin.edu.au

Post address: Food & Mood Centre, 285 Ryrie Street, 3220, Victoria, Australia

^ Co-senior author

Affiliations

1. Deakin University, Food & Mood Centre, IMPACT SRC, School of Medicine, Geelong, Australia.
2. Department of Psychiatry, Kuopio University Hospital, Kuopio, Finland
3. Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland
4. School of Psychology and Exercise Science, Murdoch University, Perth, Western Australia, Australia
5. Faculty of Health Sciences & Medicine, Bond University, Robina, Queensland, Australia
6. Deakin University, IMPACT SRC, School of Medicine, Barwon Health, Geelong Australia.
7. Department of Psychiatry; Orygen, the National Centre of Excellence in Youth Mental Health; Centre for Youth Mental Health and the Florey Institute for Neuroscience and Mental Health, University of Melbourne, Australia

This is a pre-copyedited, author-produced version of an article accepted for publication in Nutrition Reviews following peer review. The version of record Marx, W., Lane, M., Rocks, T., Ruusunen, A., Loughman, A., Lopresti, A., ... Dean, O. M. (2019). Effect of saffron supplementation on symptoms of depression and anxiety: a systematic review and meta-analysis. Nutrition Reviews, [nuz023] is available online at: https://doi.org/10.1093/nutrit/nuz023.

8. Centre for Adolescent Health, Murdoch Children's Research Institute, VIC; Australia
9. Black Dog Institute, NSW; Australia
10. Florey Institute for Neuroscience and Mental Health, University of Melbourne, Kenneth Myer Building, 30 Royal Parade, 3052, Parkville, Australia.
11. University of Melbourne, Department of Psychiatry, Level 1 North, Main Block, Royal Melbourne Hospital, Parkville, 3052, Australia

1 Abstract

Context

Saffron (Crocus sativus L.) has gained interest as a potential treatment in psychiatry.

Objective

To investigate the effect of saffron supplementation, as both an adjunctive 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.

Data Analysis

Twenty-three studies were included. Saffron had a large positive effect size when compared to 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.

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

2 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, 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 non-selective serotonin receptor agonist meta-chlorophenylpiperazine, lowering obsessive-like behaviours [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 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 both in depression and in 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.

3 Methods

3.1 Literature search

This review was written in accordance with the PRISMA (Supplementary Material 1) [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 "crocetin") 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 cross-over studies; published in English, included measures of mental health (e.g. depression, low mood, depressive symptoms, emotional problems, and anxiety), and used any component of saffron (e.g. 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.

3.2 Data extraction

Two authors (ML and AL) independently screened individual studies in duplicate with disagreements resolved by consensus or third author (WM). 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, gender, and co-morbidities), 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.

3.3 Assessment of study risk of bias

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

3.4 Statistical Analyses

The meta-analyses were conducted in Comprehensive Meta-Analysis 3.0[20] using a DerSimonian-Laird random-effects model [21] to account for heterogeneity between studies. The primary outcome was the effect of saffron on total depressive symptoms in comparison to placebo control conditions. The effect of saffron on symptoms of depression as an adjunctive to medication and as a stand-alone intervention compared to medication was also computed as a secondary outcome. The effect of saffron on symptoms of anxiety compared to 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 to

control condition as Hedges' g (with 95% confidence intervals (CI)). For studies that used more than one 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 more than one active saffron condition, a pooled effect was computed across all saffron arms compared to the non-saffron comparator conditions. To examine the possibility of publication bias affecting results, Eggers' 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 in order to recalculate effect sizes after statistically accounting for outlier studies.

Additionally, subgroup analyses were conducted to examine the (i) effects of saffron in comparison to antidepressant medications, and (ii) the effect of saffron on depression when used as an adjunctive treatment alongside antidepressants (i.e. 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 inter-study differences, rather than due to chance.

4 Results

4.1 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).

4.2 Study Characteristics

A total of 1237 participants were enrolled in the included studies, with 30 to 128 participants in each study. Trials ran from 4 to 12 weeks with 6 weeks being the most common trial

length (9/23). Seventeen studies investigated saffron monotherapy (n=11 studies) or as an adjunctive pharmacotherapy compared to placebo (n=6 studies). Six studies compared saffron monotherapy to an antidepressant medication (including fluoxetine,[22-25] imipramine,[26] and citalopram [27]). No study investigated saffron as an adjunct to psychotherapy. Nineteen studies included participants with either clinical diagnosis of mental illness or had clinical symptoms of mental illness using a validated tool. The average age of participants was 39 years with a range of 14 to 57 years. Most studies included a mix of genders with 5 studies including only females and 1 study including only males. Most studies were conducted in Iran (21/23) with two studies conducted in Australia [28,29]. Thirteen studies were conducted by the same research group. Risk of bias across most studies was low with 20 studies receiving a score between 4 and 5 (out of 5) on the Jadad Scale (Supplementary Material 2).

4.3 Interventions

Most studies (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. Nine studies reported that the intervention was standardized to contain either crocin, safranal, or lepticrosalides® (a measure of bioactive compounds present in saffron, including safranal and crocin isomers).

4.4 Outcome measures

Depressive symptoms (22/23) were more commonly investigated than anxiety symptoms (8/23). Depression and/or anxiety symptoms were measured using either 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.

4.5 Study Results

4.5.1 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 to placebo (g=0.99, 95% CI=0.61 to 1.37, n=14 studies, n=716 participants, $p<0.001$; Figure 2). An additional study that could not be entered into the meta-analysis due to insufficient available data also reported saffron to significantly improve depressive symptoms compared to placebo [30]. There was significant heterogeneity across the study data (Q=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 Supplementary Material 3. Correcting for publication bias using a trim-and-fill analysis increased the effect size of saffron supplementation (g=1.14, 95% CI=0.74 to 1.52).

When compared to antidepressants medications, there was no significant difference between saffron and medications (g=-0.17, 95% CI=0.50 to 0.17, n=5 studies, n=210 participants, p=0.33; Figure 2). There was a low degree of heterogeneity across the study data (Q=6.16, p=0.19, I^2 =35.1%). One study that did not report sufficient information to be included in the meta-analysis also reported no significant difference in depressive symptoms between saffron and medication [23].

Meta-analysis of studies that investigated the effect of saffron as an adjunct to pharmacotherapy (i.e. 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 to 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) [31].

4.5.2 Effects of Saffron on Symptoms of Anxiety

Figure 3 displays the effects of saffron mono and adjunctive therapy on symptoms of anxiety across 6 RCTs compared to placebo (n=375 participants). Random-effects meta-analysis found a large positive effect size for saffron on reducing symptoms of anxiety in comparison to placebo control conditions (g=0.95, 95% CI=0.27 to 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 to 2.150). There were insufficient studies to conduct a meta-analysis of the effect of saffron on anxiety in comparison to 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 to citalopram reported no significant difference between treatment groups [27].

4.5.3 Sensitivity Analyses

Sensitivity analyses were performed to exclude one outlier study that could be influencing the overall findings [32]. Exclusion of this study only slightly reduced the overall effect size of saffron on depressive symptoms compared to placebo (g=0.84, 95% CI=0.53 to 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 (Eggers regression intercept = 4.957, p=0.043).

When performing sensitivity analyses with the outlier study excluded for anxiety outcomes, the effects of saffron compared to placebo were reduced substantially, although overall

results remained the same (g=0.48, 95% CI=0.25 to 0.70, p<0.001). There was also little indication of heterogeneity (Q=3.39, p=0.50, I^2=0%) or publication bias (Eggers 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 a number of studies.

4.5.4 Effects of Saffron on Additional Outcomes

One study reported a significant improvement in total score of mood disturbances (p<0.001) and subscales of fatigue (p=0.007), tension (p=0.025), vigour (p=0.007), confusion (p=0.001), negative affect (p=0.001), and stress (p<0.001) when saffron supplementation was compared to placebo [28]. Another study reported significant improvements in self-reported measures of internalising symptoms (p=0.049), separation anxiety (p=0.003), and social phobia (p=0.023) compared to placebo [29]. General mental health was improved in one study compared to placebo (p<0.001) [32] and the emotional functioning subscale of a quality of life questionnaire also improved in a separate study after saffron supplementation compared to placebo (p<0.001) [33].

4.6 Adverse events

Most studies (21/23) reported on adverse events. Headache, nausea, anxiety, constipation, dry mouth, and appetite changes were the most commonly reported symptoms in both arms. No study reported symptoms occurring in the saffron group at a statistically higher rate compared to both placebo and medication.

5 Discussion

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

adolescent, and sub-clinical 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 two prior meta-analyses that investigated saffron for mild-to-major depression only [16,17]. Saffron had a significant large positive effect size when compared to placebo for both depression and anxiety outcomes. For depressive outcomes, saffron also had a significant large positive effect size when used as an adjunctive treatment to antidepressants and when compared against antidepressant medications, there was no significant difference between groups. The included studies demonstrate that saffron supplementation appears to be well-tolerated with few adverse events being reported within the included studies or by other authors [34]. 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) [35]. However, the five trials directly comparing saffron to antidepressant medication reported no statistically significant difference (p=0.33). Due to the large effect sizes, the significant publication bias detected for both outcomes, and the majority of trials being conducted in one region, many by the same research group (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 rigour regarding Good Manufacturing Practice and standardization, dosage and characterization of the active ingredients is needed.

In addition to the need to replicate existing studies, there are additional areas recommended for future studies. First, the use of saffron for other mental illnesses is currently underexplored. While seven studies assessed anxiety symptoms, only one study included participants with a diagnosed anxiety disorder. Similarly, one study evaluated the safety and feasibility of saffron in schizophrenia, but no efficacy trials have been conducted to date [36]. Furthermore, there is a need to explore comparative efficacy of the different components of saffron. One study reported that saffron petal and stigma had equivalent efficacy in treating depressive symptoms in participants with major depression but there is insufficient literature to comment on particular components at this stage [37]. Due to the high cost of saffron for culinary use, previous reviews have recommended the investigation of the efficacy of less expensive parts of saffron (e.g. petal and corm) [4]. However, due to 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, 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 of these biological markers and clinical symptoms. Furthermore, as demonstrated by Rapaport et al.[38], who reported that treatment response to omega-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 30mg

per day of saffron; however, it is unclear if there are other regimens that may improve the therapeutic effect.

6 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 significant risk of publication bias among the many small- scale pilot trials published on this topic. Indeed, the large effect sizes reported in 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, as well as the efficacy in diagnosed mental illnesses are also required.

7 Acknowledgments

We would like to acknowledge Dr Joe Firth and Professor Jerome Sarris for their contribution on aspects of the analyses and interpretation for the initial version of the manuscript. OMD would like to acknowledge the support of the National Health and Medical Research Council for providing a Career Development (2) Fellowship (APP1145634).

8 Funding declaration

No funding was provided for the development of this manuscript. **WM** is supported by a Deakin University research fellowship. **TR** is supported by a Fernwood Foundation Fellowship. **AR** is supported by a Deakin University research fellowship. **AL** is supported by the Wilson Foundation. **MB** is supported by a National Health and Medical Research Council (NHMRC) Senior Principal Research Fellowship (grant number 1059660). **FNJ** has received

Grant/Research support from the Brain and Behaviour Research Institute, the National Health and Medical Research Council (NHMRC), Australian Rotary Health, the Geelong Medical Research Foundation, the Ian Potter Foundation, Eli Lilly, Meat and Livestock Australia, Woolworths Limited, Fernwood Gyms, The Wilson Foundation, GMHBA and The University of Melbourne and has received speakers honoraria from Sanofi-Synthelabo, Janssen Cilag, Servier, Pfizer, Health Ed, Network Nutrition, Angelini Farmaceutica, Eli Lilly and Metagenics. FNJ is supported by an NHMRC Career Development Fellowship (2) (#1108125). FNJ is currently writing two books for commercial publication and has a personal belief that good diet quality is important for mental and brain health. **OMD** is a R.D. Wright Biomedical Research Fellow and has received grant support from the Brain and Behavior Foundation, Simons Autism Foundation, Stanley Medical Research Institute, Deakin University, Lilly, NHMRC and ASBDD/Servier. She has also received in kind support from BioMedica Nutracuticals, NutritionCare and Bioceuticals.

Author Contributions

All authors contributed to final manuscript. WM led all stages of the manuscript. ML and AL conducted the data extraction. SM conduct the risk of bias assessment. TR, ML and AR extracted the data from included studies. ALopresti contributed to the mechanisms discussion and background.

References

1. Maes M, Leonard B, Fernandez A, et al. (Neuro)inflammation and neuroprogression as new pathways and drug targets in depression: from antioxidants to kinase inhibitors. *Progress in Neuro-psychopharmacology & Biological Psychiatry.* 2011;35(3):659-663.
2. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol.* 2015;16(1):22-34.
3. Moylan S, Maes M, Wray NR, Berk M. The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. *Molecular psychiatry.* 2013;18(5):595-606.
4. Lopresti AL, Drummond PD. Saffron (Crocus sativus) for depression: a systematic review of clinical studies and examination of underlying antidepressant mechanisms of action. *Hum Psychopharmacol.* 2014;29(6):517-527.
5. Ettehadi H, Mojabi SN, Ranjbaran M, et al. Aqueous Extract of Saffron (Crocus sativus) Increases Brain Dopamine and Glutamate Concentrations in Rats. *Journal of Behavioral and Brain Science.* 2013;3(3):315-319.
6. Georgiadou G, Tarantilis PA, Pitsikas N. Effects of the active constituents of Crocus Sativus L., crocins, in an animal model of obsessive-compulsive disorder. *Neuroscience letters.* 2012;528(1):27-30.
7. Razavi M, Hosseinzadeh H, Abnous K, Motamedshariaty VS, Imenshahidi M. Crocin restores hypotensive effect of subchronic administration of diazinon in rats. *Iran J Basic Med Sci.* 2013;16(1):64-72.
8. Boskabady MH, Farkhondeh T. Antiinflammatory, Antioxidant, and Immunomodulatory Effects of Crocus sativus L. and its Main Constituents. *Phytother Res.* 2016;30(7):1072-1094.
9. Samarghandian S, Nezhad MA, Samini F, Farkhondeh T. The role of saffron in attenuating age-related oxidative damage in rat hippocampus. *Recent Pat Food Nutr Agric.* 2017.
10. Poma A, Fontecchio G, Carlucci G, Chichiricco G. Anti-inflammatory properties of drugs from saffron crocus. *Anti-inflammatory & anti-allergy agents in medicinal chemistry.* 2012;11(1):37-51.
11. Boskabady MH, Seyedhosseini Tamijani SM, Rafatpanah H, Rezaei A, Alavinejad A. The effect of Crocus sativus extract on human lymphocytes' cytokines and T helper 2/T helper 1 balance. *Journal of medicinal food.* 2011;14(12):1538-1545.
12. Halataei BA, Khosravi M, Arbabian S, et al. Saffron (Crocus sativus) aqueous extract and its constituent crocin reduces stress-induced anorexia in mice. *Phytotherapy research : PTR.* 2011;25(12):1833-1838.
13. Hooshmandi Z, Rohani AH, Eidi A, Fatahi Z, Golmanesh L, Sahraei H. Reduction of metabolic and behavioral signs of acute stress in male Wistar rats by saffron water extract and its constituent safranal. *Pharmaceutical biology.* 2011;49(9):947-954.
14. Vahdati Hassani F, Naseri V, Razavi BM, Mehri S, Abnous K, Hosseinzadeh H. Antidepressant effects of crocin and its effects on transcript and protein levels of CREB, BDNF, and VGF in rat hippocampus. *Daru.* 2014;22(1):16.
15. Ghasemi T, Abnous K, Vahdati F, Mehri S, Razavi BM, Hosseinzadeh H. Antidepressant Effect of Crocus sativus Aqueous Extract and its Effect on CREB, BDNF, and VGF Transcript and Protein Levels in Rat Hippocampus. *Drug Res (Stuttg).* 2014. http://www.ncbi.nlm.nih.gov/pubmed/24696423. Accessed Apr 2.
16. Hausenblas HA, Saha D, Dubyak PJ, Anton SD. Saffron (Crocus sativus L.) and major depressive disorder: a meta-analysis of randomized clinical trials. *Journal of integrative medicine.* 2013;11(6):377-383.

17. Yang X, Chen X, Fu Y, et al. Comparative efficacy and safety of Crocus sativus L. for treating mild to moderate major depressive disorder in adults: a meta-analysis of randomized controlled trials. *Neuropsychiatr Dis Treat.* 2018;14:1297-1305.
18. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *PLOS Medicine.* 2009;6(7):e1000100.
19. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled clinical trials.* 1996;17(1):1-12.
20. *Comprehensive meta-analysis version 3* [computer program]. Englewood, NJ: Biostat 104 2011.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials.* 1986;7(3):177-188.
22. Akhondzadeh Basti A, Moshiri E, Noorbala AA, Jamshidi AH, 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. *Progress in Neuro-Psychopharmacology and Biological Psychiatry.* 2007;31(2):439-442.
23. Kashani L, Eslatmanesh S, Saedi N, et al. Comparison of Saffron versus Fluoxetine in Treatment of Mild to Moderate Postpartum Depression: A Double-Blind, Randomized Clinical Trial. *Pharmacopsychiatry.* 2017;50(2):64-68.
24. Noorbala A, Akhondzadeh S, Tahmacebi-Pour N, Jamshidi A. Hydro-alcoholic extract of Crocus sativus L. versus fluoxetine in the treatment of mild to moderate depression: a double-blind, randomized pilot trial. *Journal of ethnopharmacology.* 2005;97(2):281-284. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/149/CN-00508149/frame.html.
25. Shahmansouri N, Farokhnia M, Abbasi S, et al. A randomized, double-blind, clinical trial comparing the efficacy and safety of Crocus sativus L. with fluoxetine for improving mild to moderate depression in post percutaneous coronary intervention patients. *Journal of affective disorders.* 2014;155:216-222. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/884/CN-00959884/frame.html.
26. Akhondzadeh S, Fallah-Pour H, Afkham K, Jamshidi AH, 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 complementary and alternative medicine.* 2004;4 (no pagination)(12).
27. Ghajar A, Neishabouri SM, Velayati N, et al. Crocus sativus L versus Citalopram in the Treatment of Major Depressive Disorder with Anxious Distress: A Double-Blind, Controlled Clinical Trial. *Pharmacopsychiatry.* 2017;50(4):152-160.
28. Kell G, Beccaria G, Rao A, Clayton P, Inarejos-García AM, Prodanov M. affron® a novel saffron extract (Crocus sativus L.) improves mood in healthy adults over 4 weeks in a double-blind, parallel, randomized, placebo-controlled clinical trial. *Complementary Therapies in Medicine.* 2017;33:58-64.
29. Lopresti AL, Drummond PD, Inarejos-Garcia AM, Prodanov M. affron((R)), a standardised extract from saffron (Crocus sativus L.) for the treatment of youth anxiety and depressive symptoms: A randomised, double-blind, placebo-controlled study. *Journal of affective disorders.* 2018;232:349-357.
30. Tabeshpour J, Sobhani F, Sadjadi SA, et al. A double-blind, randomized, placebo-controlled trial of saffron stigma (Crocus sativus L.) in mothers suffering from mild-to-moderate postpartum depression. *Phytomedicine.* 2017;36:145-152.
31. Sahraian A, Jelodar S, Javid Z, Mowla A, Ahmadzadeh L. Study the effects of saffron on depression and lipid profiles: A double blind comparative study. *Asian Journal of Psychiatry.* 2016;22:174-176.

32. Talaei A, Hassanpour Moghadam M, Sajadi Tabassi SA, Mohajeri SA. Crocin, the main active saffron constituent, as an adjunctive treatment in major depressive disorder: A randomized, double-blind, placebo-controlled, pilot clinical trial. *Journal of affective disorders.* 2015;174:51-56.
33. Abedimanesh N, Ostadrahimi A, Bathaie SZ, et al. Effects of saffron aqueous extract and its main constituent, crocin, on health-related quality of life, depression, and sexual desire in coronary artery disease patients: A double-blind, placebo-controlled, randomized clinical trial. *Iranian Red Crescent Medical Journal.* 2017;19 (9) (no pagination)(e13676).
34. Modaghegh MH, Shahabian M, Esmaeili HA, Rajbai O, Hosseinzadeh H. Safety evaluation of saffron (Crocus sativus) tablets in healthy volunteers. *Phytomedicine.* 2008;15(12):1032-1037.
35. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet (London, England).* 2018;391(10128):1357-1366.
36. Moosavi S, Ahmadi M, Amini M, Vazirzadeh B. The effects of 40 and 80 mg hydro- alcoholic extract of crocus sativus in the treatment of mild to moderate depression. *Journal of mazandaran university of medical sciences.* 2014;24(113):47-53. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/117/CN-00999117/frame.html.
37. Akhondzadeh Basti A, Moshiri E, Noorbala AA, Jamshidi AH, 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. *Progress in neuro-psychopharmacology & biological psychiatry.* 2007;31(2):439-442.
38. Rapaport MH, Nierenberg AA, Schettler PJ, et al. Inflammation as a Predictive Biomarker for Response to Omega-3 Fatty Acids in Major Depressive Disorder: A Proof of Concept Study. *Molecular psychiatry.* 2016;21(1):71-79.
39. Akhondzadeh S, Tahmacebi-Pour N, Noorbala A, et al. Crocus sativus L. in the treatment of mild to moderate depression: a double-blind, randomized and placebo-controlled trial. *Phytotherapy Research.* 2005;19(2):148-151.
40. Agha-Hosseini M, Kashani L, Aleyaseen A, et al. Crocus sativus L. (saffron) in the treatment of premenstrual syndrome: a double-blind, randomised and placebo-controlled trial. *BJOG : an international journal of obstetrics and gynaecology.* 2008;115(4):515-519.
41. Jafarnia N, Ghorbani Z, Nokhostin M, Manayi A, Nourimajd S, Jahromi SR. Effect of saffron (Crocus sativus L.) as an add-on therapy to sertraline in mild to moderate generalized anxiety disorder: A double blind randomized controlled trial. *Archives of Neuroscience.* 2017;4 (4) (no pagination)(e14332).
42. Jam IN, Sahebkar AH, Eslami S, et al. The effects of crocin on the symptoms of depression in subjects with metabolic syndrome. *Advances in Clinical and Experimental Medicine.* 2017;26(6):925-930.
43. Jelodar G, Javid Z, Sahraian A, Jelodar S. Saffron improved depression and reduced homocysteine level in patients with major depression: A Randomized, double-blind study. *Avicenna Journal of Phytomedicine.* 2018;8(1):43-50.
44. Kashani L, Esalatmanesh S, Eftekhari F, et al. Efficacy of Crocus sativus (saffron) in treatment of major depressive disorder associated with post-menopausal hot flashes: a double-blind, randomized, placebo-controlled trial. *Archives of Gynecology and Obstetrics.* 2018;297(3):717-724.
45. Kashani L, Raisi F, Saroukhani S, et al. Saffron for treatment of fluoxetine-induced sexual dysfunction in women: randomized double-blind placebo-controlled study. *Human psychopharmacology.* 2013;28(1):54-60. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/835/CN-00861835/frame.html.

46. Mazidi M, Shemshian M, Mousavi SH, et al. A double-blind, randomized and placebo-controlled trial of Saffron (Crocus sativus L.) in the treatment of anxiety and depression. *Journal of Complementary and Integrative Medicine.* 2016;13(2):195-199.
47. Moazen-Zadeh E, Abbasi SH, Safi-Aghdam H, et al. Effects of Saffron on Cognition, Anxiety, and Depression in Patients Undergoing Coronary Artery Bypass Grafting: A Randomized Double-Blind Placebo-Controlled Trial. *Journal of alternative and complementary medicine (New York, NY).* 2017.
48. Modabbernia A, Sohrabi H, Nasehi A, et al. Effect of saffron on fluoxetine-induced sexual impairment in men: randomized double-blind placebo-controlled trial. *Psychopharmacology.* 2012;223(4):381-388. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/596/CN-00850596/frame.html.
49. Moshiri E, Basti A, Noorbala A, Jamshidi A, Hesameddin AS, 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. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/244/CN-00572244/frame.html.

Figure 1. PRISMA flow chart of study selection

Figure 2. Meta-analysis showing effects of saffron on symptoms of depression in (a) comparison to antidepressant medications, and (b) comparison to 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.

Supplementary Information

Supplement 1. PRISMA Checklist

Supplement 2. Risk of bias summaries for included studies.

Supplement 3. Forest-plot of publication bias

Table 1. PICOS criteria for inclusion and exclusion of studies

Domain	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

Table 2. Summary table of included studies

Author/ Date	Study details	Population details	Intervention (mgs per day)	Outcomes*	Results
Abedimanesh et al. (2017)[33]	**Study design:** Randomized, double blind, placebo controlled **Country:** Iran **Sample size (n):** 63 enrolled, 58 completed **Total study period:** 8 weeks	Male and female Coronary Artery Disease (CAD) patients **Age in years (average):** 55	30 mg SAE, Saffron Aqueous Extract (stigma) OR 30 mg Crocin (stigma) OR Placebo	**Outcomes measured:** Depression measured using BDI-II **Outcomes measured at:** Baseline and after 8 weeks of intervention	The BDI-II score significantly decreased in the SAE and Crocin groups compared to Placebo from baseline to endpoint ($P < 0.001$). No significant difference between the Crocin and SAE groups in total BDI-II score at endpoint ($P = 0.999$).
Akhondzadeh Basti et al. (2007)[22]	**Study design:** Randomized, double blind, parallel group	Male and female outpatients who met DSM-IV criteria for major	30 mg Saffron (petal) OR 20 mg Fluoxetine	**Outcomes measured:** Depression measured using HAM-D-17	The HAM-D-17 score significantly decreased in both the Saffron and Fluoxetine groups from

	Country: Iran **Sample size:** 40 enrolled, 38 completed **Total study period:** 8 weeks	depression based on the SCID-IV **Age in years (average):** 34		**Outcomes measured at:** Baseline, week 1, week 2, week 4, week 6 and week 8 (endpoint)	baseline to endpoint ($P <$ 0.001). No significant difference at endpoint between the two groups (P = 0.84).
Akhondzadeh et al. (2005)[39]	**Study design:** Randomized, double blind, parallel group **Country:** Iran **Sample size:** 40 enrolled, 35 completed **Total study period:** 6 weeks	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 (stigma) OR Placebo	**Outcomes measured:** Depression measured using HAM-D-17 **Outcomes measured at:** Baseline, week 1, week 2, week 4 and week 6 (endpoint)	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 to Placebo ($P <$ 0.001).

Akhondzadeh et al. (2004)[26]	**Study design:** Randomized, double blind, parallel group **Country:** Iran **Sample size:** 30 enrolled, 30 completed **Total study period:** 6 weeks	Male and female outpatients who met DSM-IV criteria for major depression based on the SCID-IV **Age in years (average):** 34	30 mg Saffron (stigma) OR 100 mg Imipramine	**Outcomes measured:** Depression measured using HAM-D-17 **Outcomes measured at:** Baseline, week 1, week 2, week 3, week 4, week 5 and week 6 (endpoint)	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 two groups ($P = 0.09$).
Agha-Hosseini et al. (2008) [40]	**Study design:** Randomized, double blind, placebo controlled **Country:** Iran **Sample size:** 50 enrolled, 47 completed	Women with regular menstrual cycles and experience of PMS symptoms for at least 6 months **Age in years (average):** 34	30 mg Saffron (petal) OR Placebo	**Outcomes measured:** Depression measured using HAM-D-17 PMS factors including mood (e.g. anxiety, irritability, depression, nervous tension, mood	The HAM-D-17 score significantly decreased in the Saffron group compared to Placebo from baseline to endpoint ($P < 0.001$). The total Daily Symptom Report Checklist score significantly decreased in

	Total study period: 8 weeks; or two menstrual cycles (cycles 3 and 4)			swings and out of control) measured using Daily Symptom Report Checklist **Outcomes measured at:** Baseline (i.e. at the end of cycle 2, a premenstrual stage—as close as possible to 2 days prior to the onset of menstruation) and the premenstrual stage of cycles 3 and 4.	the Saffron group compared to Placebo from baseline to endpoint, (P = 0.002).
Ghajar et al. (2017)[27]	**Study design:** Randomized, double blind, parallel group **Country:** Iran	Male and female patients who met DSM-IV criteria for mild-to-moderate major depression coupled with anxious distress	30 mg Saffron (stigma) OR 40 mg Citalopram	**Outcomes measured:** Depression measured using HAM-D-17	The HAM-D-17 and HAM-A scores significantly decreased in both the Saffron and Citalopram groups from baseline to

	Sample size: 66 enrolled, 60 completed **Total study period:** 6 weeks	**Age in years (average):** 36		Anxiety measured using HAM-A **Outcomes measured at:** Baseline, week 2, week 4 and week 6 (endpoint)	endpoint ($P < 0.001$). No significant difference for either HAM-D-17 or HAM-A scores at endpoint between the two groups (P 0.715 and $P = 0.999$, respectively).
Jafarnia et al. (2017)[41]	**Study design:** Randomized, double blind, placebo controlled **Country:** Iran **Sample size:** 40 enrolled, 40 completed **Total study period:** 6 weeks	Male and female patients who met DSM-IV criteria for mild-to-moderate Generalised Anxiety Disorder (GAD) and were receiving Sertraline **Age in years (average):** 31	500 mg capsule containing 450 mg Saffron (type not recorded) AND 50 mg Sertraline OR Placebo AND 50 mg Sertraline	**Outcomes measured:** Anxiety measured using HAM-A **Outcomes measured at:** Baseline, week 3 and week 6 (endpoint)	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 to Placebo (coupled with Sertraline), ($P < 0.005$).
Jam et al. (2017)[42]	**Study design:** Randomized, double blind, placebo controlled **Country:** Iran **Sample size:** 34 enrolled, 33 completed **Total study period:** 8 weeks	Male and female patients with Metabolic Syndrome (MetS) and depressive symptoms based on the BDI **Age in years (average):** 46	30 mg Saffron (crocin) OR Placebo	**Outcomes measured:** Depression measured using BDI **Outcomes measured at:** Baseline and week 8 (endpoint)	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 two groups ($P = 0.013$).
Jelodar et al. (2018)[43]	**Study design:** Randomized, double blind, placebo controlled **Country:** Iran	Male and female outpatients who met DSM-IV criteria for major	30 mg Saffron (stigma) AND 20 mg Fluoxetine OR Placebo AND 20 mg Fluoxetine	**Outcomes measured:** Depression measured using BDI	The BDI score significantly decreased in both the Saffron (coupled with Fluoxetine) and Placebo

	Sample size: 40 enrolled, 40 completed **Total study period:** 4 weeks	depression based on the SCID-IV **Age in years (range):** 20 to 55		**Outcomes measured at:** Baseline and week 4 (endpoint)	(coupled with Fluoxetine) groups from baseline to endpoint ($P < 0.05$). No significant difference at endpoint between the two groups ($P < 0.056$).
Kashani et al. (2018)[44]	**Study design:** Randomized, double blind, placebo controlled **Country:** Iran **Sample size:** 60 enrolled, 56 completed **Total study period:** 6 weeks	Women who met DSM-IV criteria for major depression and mild-to-moderate depression based on HDRS as well as post-menopausal hot flashes **Age in years (average):** 55	30 mg Saffron (stigma) OR Placebo	**Outcomes measured:** Depression measured using HDRS **Outcomes measured at:** Baseline, week 2, week 4 and week 6 (endpoint)	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 to Placebo ($P < 0.001$).

Kashani et al. (2017)[23]	**Study design:** Randomized, double blind, parallel group **Country:** Iran **Sample size:** 68 enrolled, 64 completed **Total study period:** 6 weeks	Women who met DSM-IV criteria for post-partum depression 4-12 weeks after childbirth as well as scoring > 10 and < 18 on HDRS **Age in years (average):** 30	30 mg Saffron (stigma) OR 20 mg Fluoxetine	**Outcomes measured:** Depression measured using HDRS **Outcomes measured at:** Baseline, week 1, week 3 and week 6 (endpoint)	*Significance of reduction in HDRS score within groups for Saffron and Fluoxetine from baseline to endpoint not recorded. No significant difference at endpoint between the two groups ($P = 0.37$).
Kashani et al. (2013)[45]	**Study design:** Randomized, double blind, placebo controlled **Country:** Iran **Sample size:** 38 enrolled, 34 completed	Female outpatients who met DSM-IV criteria for major depression; were being treated with 40 mg / day of Fluoxetine for at least 6 weeks prior to entry; and, whose depressive symptoms had been stabilised (i.e. 50%	30 mg Saffron (petal) AND 40 mg Fluoxetine OR Placebo AND 40 mg Fluoxetine	**Outcomes measured:** Depression measured using HDRS **Outcomes measured at:** Baseline, week 2 and week 4 (endpoint)	*Significance of reduction in HDRS score within groups for Saffron (coupled with Fluoxetine) and Placebo (coupled with Fluoxetine) from baseline to endpoint not recorded.

	Total study period: 4 weeks	reduction in depression score) **Age in years (average):** 35			No significant difference at endpoint between the two groups ($P = 0.278$).
Kell et al. (2017)[28]	**Study design:** Randomized, double blind, parallel group, placebo controlled **Country:** Australia **Sample size:** 128 enrolled, 121 completed **Total study period:** 4 weeks	Male and females self-reporting low mood but not diagnosed with depression or another mood disorder and who were otherwise healthy **Age in years (average):** 39	28 mg Saffron (stigma) OR Saffron 22 mg (stigma) Saffron OR Placebo	**Outcomes measured:** Mood measured using POMS, Profile of Mood State; and, PANAS-21, Positive and Negative Affect Schedule Depression, anxiety and stress measured using DASS-21, Depression, Anxiety and Stress Scale **Outcomes measured at:** Baseline and week 4 (endpoint)	The POMS Total Mood Disturbance score significantly decreased for the 28 mg Saffron group compared to Placebo at endpoint ($P < 0.001$). No treatment effect on the POMS Total Mood Disturbance score for the 22mg Saffron group. The PANAS-21 score for Positive Affect showed no significant difference at endpoint between the three

					groups regarding (P = 0.124). However, the PANAS-21 score for Negative Affect significantly decreased for the 28 mg Saffron group compared to Placebo at endpoint ($P < 0.001$). The DASS-21 score for depression decreased significantly more for the 28 mg Saffron group compared to both 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). The DASS-21 score for anxiety significantly decreased for the 28 mg Saffron group compared to Placebo at endpoint (P < 0.010). No significant difference between 22 mg Saffron group compared to 28 mg Saffron or Placebo groups at end point (P = 0.149 and P = 0.625, respectively). The DASS-21 score for stress significantly decreased for the 28 mg Saffron group compared to

					both the 22 mg Saffron and Placebo groups at endpoint ($P < 0.001$ and $P = 0.001$, respectively).
Lopresti et al. (2018)[29]	**Study design:** Randomized, double blind, placebo controlled **Country:** Australia **Sample size:** 80 enrolled, 68 completed **Total study period:** 8 weeks	Male and female youth who were assessed as suffering from mild-to-moderate anxiety and depressive symptoms **Age in years (average):** 14	14 mg Saffron (stigma) OR Placebo	**Outcomes measured:** Depression and anxiety measured using youth and parent reports for RCADS, Revised Child Anxiety and Depression Scale. Subscales: separation anxiety; generalised anxiety; panic; social phobia; obsessions/compulsions; depression	**Youth reports:** The total RCADS score significantly decreased from baseline to endpoint for the Saffron group compared to Placebo $P < 0.049$), and three subscale scores: separation anxiety ($P = 0.003$); social phobia ($P = 0.023$); and, depression ($P = 0.016$). **Parent reports:** No significant difference from baseline to endpoint for total RCADS scores

				Outcomes measured at: Baseline, week 2, week 4, week 6 and week 8 (endpoint)	between groups (P = 0.749). Saffron had a significant mean improvement (P = 0.026), and in two subscales from baseline to endpoint: generalised anxiety (P < 0.01); and, obsessions/ compulsions (P < 0.01).
Mazidi et al. (2016)[46]	**Study design:** Randomized, double blind, placebo controlled **Country:** Iran **Sample size:** 60 enrolled, 54 completed	Male and female patients who met DSM-IV criteria for mild-to-moderate mixed anxiety and depression based on the SCID-IV **Age in years (average):** 43	100 mg Saffron (stigma) OR Placebo	**Outcomes measured:** Depression measured using BDI Anxiety measured using BAI	The BDI and BAI scores significantly decreased in the Saffron group compared to Placebo from baseline to endpoint (P < 0.001).

	Total study period: 12 weeks			**Outcomes measured at:** Baseline, week 3, week 6, and week 12 (endpoint).	
Moazen-Zadeh et al. (2017)[47]	**Study design:** Randomized, double blind, placebo controlled **Country:** Iran **Sample size:** 76 enrolled, 37 completed **Total study period:** 12 weeks	Male and female patients referred for on-pump coronary artery bypass grafting surgery with WMS-R, Wechsler Memory Scale-Revised score > 70 and age < 70. Enrolled to receive Saffron or Placebo from 2 days before surgery up to 12 weeks after. **Age in years (average):** 57	30 mg Saffron (stigma) OR Placebo	**Outcomes measured:** Anxiety and Depression measured using HADS, Hospital Anxiety and Depression Scale **Outcomes measured at:** Baseline and week 12 (endpoint)	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).

Modabbernia et al. (2012)[48]	**Study design:** Randomized, double blind, placebo controlled **Country:** Iran **Sample size:** 36 enrolled, 30 completed **Total study period:** 4 weeks	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 weeks prior to entry). **Age in years (average):** 38	30 mg Saffron (stigma) AND 40 mg Fluoxetine OR Placebo AND 40 mg Fluoxetine	**Outcomes measured:** Depression measured using HDRS **Outcomes measured at:** Baseline and week4 (endpoint)	No significant difference from baseline to endpoint for HDRS scores between Saffron (coupled with Fluoxetine) and Placebo (coupled with Fluoxetine) groups ($P = 0.178$).
Moshiri et al. (2006)[49]	**Study design:** Randomized, double blind, placebo controlled **Country:** Iran **Sample size:** 40 enrolled, 36 completed	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 weeks prior to entry.	30 mg Saffron (petal) OR Placebo	**Outcomes measured:** Depression measured using HAM-D-17 **Outcomes measured at:** Baseline, week 1, week 2, week 4 and week 6 (endpoint)	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

	Total study period: 6 weeks	**Age in years (average):** 35			compared to Placebo ($P < 0.001$)
Noorbala et al. (2005)[24]	**Study design:** Randomized, double blind, parallel group **Country:** Iran **Sample size:** 40 enrolled, 38 completed **Total study period:** 6 weeks	Male and female outpatients who met DSM-IV criteria for mild-to-moderate depression based on the SCID-IV **Age in years (average):** 36	30 mg Saffron (stigma) OR 20 mg Fluoxetine	**Outcomes measured:** Depression measured using HAM-D-17 **Outcomes measured at:** Baseline, week 1, week 2, week 4 and week 6 (endpoint)	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 two groups ($P = 0.71$).
Sahraian et al. (2016)[31]	**Study design:** Randomized, double blind, placebo controlled **Country:** Iran	Male and female outpatients who met DSM-IV criteria for major depression based on the SCID-IV	30 mg Saffron (type not recorded) AND 20 mg Fluoxetine OR Placebo AND 20 mg Fluoxetine	**Outcomes measured:** Depression measured using BDI	The BDI score significantly decreased in both the Saffron (coupled with Fluoxetine) and Placebo (coupled with Fluoxetine)

	Sample size: 40 enrolled, 30 completed **Total study period:** 4 weeks	**Age in years (average):** 43		**Outcomes measured at:** Baseline and week 4 (endpoint)	groups from baseline to endpoint ($P < 0.003$ and $P < 0.000$. respectively). No significant difference at endpoint between the two groups ($P = 0.560$).
Shahmansouri et al. (2013)[25]	**Study design:** Randomized, double blind, parallel group **Country:** Iran **Sample size:** 44 enrolled, 40 completed **Total study period:** 6 weeks	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 undergone Percutaneous Coronary Intervention (PCI) in the last 6 months **Age in years (average):** 53	30 mg Saffron (stigma) OR 40 mg Fluoxetine	**Outcomes measured:** Depression measured using HDRS **Outcomes measured at:** Baseline, week 3 and week 6 (endpoint)	The HDRS score significantly decreased in both the Saffron and Fluoxetine groups from baseline to endpoint. No significant difference at endpoint between the two groups ($P = 0.70$).

Tabeshpour et al. (2017)[30]	**Study design:** Randomized, double blind, placebo controlled **Country:** Iran **Sample size:** 78 enrolled, 60 completed **Total study period:** 8 weeks	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, week 4 and week 8 (endpoint)	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 to Placebo ($P < 0.001$).
Talaei et al. (2015)[32]	**Study design:** Randomized, double blind, placebo controlled **Country:** Iran **Sample size:** 46 enrolled, 40 completed	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 20mg Fluoxetine; OR 50mg Sertraline; OR 20mg Citalopram -OR-	**Outcomes measured:** Depression measured using BDI Anxiety measured using BAI	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

	Total study period: 4 weeks		Placebo AND 20mg Fluoxetine; OR 50mg Sertraline; OR 20mg Citalopram	Bipolar Disorder measured using MDQ, Mood Disorder Questionnaire **Outcomes measured at:** Baseline and week 4 (endpoint)	compared to Placebo ($P <$ 0.0001). *Data for MDQ not reported

*Only outcomes of interest (e.g. depression and anxiety symptoms) were extracted and are presented.