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ORIGINAL RESEARCH

The efficacy of *Crocus sativus* (Saffron) versus placebo and Fluoxetine in treating depression: a systematic review and meta-analysis

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Background: Depression represents a serious public health concern, imposing a high burden, both in epidemiological and clinical terms. *Crocus sativus* (Saffron) is a herbal remedy that has anti-cancer, anti-oxidant, anti-inflammatory and anti-platelet properties. However, the exact mechanisms of Saffron in treating depression are not yet clear. This study was conducted to evaluate the effectiveness of Saffron versus placebo and Fluoxetine in the treatment of depressed patients.

Methods: Different bibliographic thesauri, namely the Cochrane Library, Scopus, PubMed/MEDLINE, Centre for Reviews and Dissemination (CRD), EMBASE, and ISI/Web of Science (WoS) were searched up to May 2018. Effect sizes were computed as Standardized Mean Differences (SMD) with their 95% confidence interval (CI). To evaluate the heterogeneity among the studies, I^2 test was carried out.

Results: Eight studies were included. The SMD was −0.86 (95% CI: −1.73 to 0.00) concerning the comparison of Saffron with placebo. The SMD was found to be 0.11 (95% CI: −0.20 to 0.43) concerning the comparison of Saffron with Fluoxetine. In both sensitivity analyses, the results did not statistically change, confirming the stability of the findings.

Conclusion: The findings of this study showed that Saffron administration was well comparable with Fluoxetine and placebo.

Keywords: systematic review, meta-analysis, Saffron, Fluoxetine, depression

Introduction

Depression represents a serious public health concern, imposing a high burden, both in epidemiological and clinical terms.[1] This common mental disorder causes the affected person to suffer from sleep disorders, feeling tired, losing appetite, feeling grief, having guilty feelings, experiencing weakness in concentration, sadness, loss of interest in doing routine work and usual activities, among others. It can lead to suicide in extreme cases.[2,3]

According to the World Health Organization (WHO), over 300 million people worldwide are suffering from severe depression and 800,000 deaths occur due to depression-induced suicide annually.[4] The relationships between the prevalence of depression and gender, social, economic, and demographic factors have been intensively studied in various studies.[5,6]

The world's financial resources in the health sector are limited. Depression affects the working conditions of the individual, resulting in frequent absences, reduced productivity, and absenteeism. At the same time, the disease causes people to consume more health care resources.[7,8] It is estimated that by 2020, after

cardiovascular disease, depression will be the second most common cause of Disability-Adjusted Life Years (DALYs) in the world.[9] Timely diagnosis and treatment of patients with depression can play an important role in reducing disability, increasing survival and quality of life in patients, and contribute to saving the financial resources of the health sector of each country.

Different drugs can be used to treat depression, including Fluoxetine. Studies have shown its clinical effectiveness in the management of depressed patients.[10,11] On the other hand, herbal remedies, being safer and with less side-effects, can be considered as a valid alternative for the treatment of depression.[12–14]

More than 20 herbal remedies have been investigated as potential anti-depressant drugs.[15,16] *Crocus sativus* (Saffron) is one of these herbal remedies that has anti-cancer, anti-oxidant, anti-inflammatory, and anti-platelet properties.[17] Saffron can be extracted from the dried elongated stigmas and styles of saffron, a blue-purple flowering plant of the *Crocus* genus, belonging to the *Iridaceae* family, which, in some studies, has been used to treat depressed patients.[18,19]

However, the exact mechanisms of Saffron in treating depression are not yet clear. Several studies have been done to evaluate the effect of Saffron in the treatment of patients with depression. However, sometimes some contrasting findings have been reported. Therefore, using meta-analytic techniques, which enable to pool different studies together, this investigation was conducted to evaluate the effectiveness of Saffron versus placebo and Fluoxetine in the treatment of depressed patients.

Material and methods

Literature search

The results of the current review were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (10). Different bibliographic thesauri, namely the Cochrane Library, Scopus, PubMed/MEDLINE, Centre for Reviews and Dissemination (CRD), EMBASE, and ISI/Web of Science (WOS) were searched by two authors up to May 2018. The Clinical Trial, the Trial Register, as well as international congresses on depression such as the International Depressive Disorder and Anxiety Disorders and Depression were also searched.

Also, since most Saffron-related studies are performed in Iran, Iranian databases like SID, Magiran, and Irandoc were searched. Furthermore, to find relevant studies, reference lists of selected study lists were reviewed. Our search strategy was as follows: *(Saffron OR "Crocus sativus") AND (Depression OR "Major Depression Disorder" OR MDD) AND (Fluoxetine OR Placebo)*

No language, location, and time restrictions were applied. After the search was completed, all the articles found were included in the Endnote X7 software and duplicates were deleted. Then, the titles and abstracts of articles were examined based on inclusion and exclusion criteria and finally the main studies were selected. The titles and abstracts of the articles were independently reviewed by two of the authors, and in case of disagreement, discrepancies were resolved through discussion.

Inclusion and exclusion criteria

According to the Patients/Intervention/Comparator/Outcome/Study design (PICOS) criteria, inclusion criteria were the following: P (studies performed in humans and recruiting patients with an official diagnosis of depression, established according to the Diagnostic and Statistical Manual of Mental Disorders – DSM – criteria; any type of depression was considered, without any restriction with regards to the severity – mild or severe depression – or the kind of patient affected – youth or post-partum depression); I (studies in which Saffron was utilized in one arm and placebo or Fluoxetine were used in the other arm); C (Saffron versus placebo or Fluoxetine); O (effect on depression); and, S (studies designed as randomized clinical trial or RCTs).

Studies were excluded if: performed in animals or in non-depressed patients; using saffron in combination with another drug or compound; studies designed as review papers, letters to the editor, case-report and case-series; and, studies results of which were not clear or not sufficiently detailed.

Quality assessment of studies included

Quality assessment of studies included was carried out according to the Cochrane handbook.[11]

Data extraction

After finding the final studies to be included, a data extraction form was developed based on the information of the articles and the data of the articles were extracted according to the designed form. The title of the article, the name of the author of the first article, the year of the study, the year of the publication of the article, the number of participants, the measured outcomes, the reported complications, the place where the study was conducted, the date of commencement and completion of the study were extracted from each study. The studies were assessed by two authors. Any potential

disagreement was resolved through discussion or involving a third author as the referee.

Statistical analysis

Effect sizes were computed as Standardized Mean Differences (SMD) using a random-effects model with their 95% confidence interval (CI).[20] The sensitivity analysis was performed to check the stability and reliability of results. To evaluate the heterogeneity of the studies, I^2 test was carried out.[21] *P*-values less than 0.05 were considered as significant values. Due to the fact that the number of studies entered was less than 10, there was no possibility to check the publication bias. R environment (version 3.4.0) was used to analyze the data.

Results

Selected studies

The initial search yielded a pool of 157 studies, which were downloaded; after removing duplicates, 125 remained. At this stage, the title and the abstract of each study were assessed and 73 unrelated studies were discarded. The remaining 52 studies were in-depth reviewed based on the full text. Finally, according to the inclusion/exclusion criteria, 8 studies were selected. The selection process is shown in Figure S1.

Among the included studies, 4 of them compared Saffron and placebo, while four other studies compared Saffron and Fluoxetine 20 or 40 mg.[22–29] The main characteristics of these studies are presented in Table 1.

Quality of studies entered

The quality of the studies was evaluated using the Cochrane checklist (Figure S2).

Comparison of Saffron with placebo

Figure 1 shows the effect of Saffron compared to placebo. Heterogeneity among studies was computed to be 87%. The SMD was −0.86 (95% CI: −1.73 to 0.00). Stratifying on the basis of saffron doses, SMDs were computed to be −0.71 (95% CI: −2.67 to 1.26) and −1.01 (95% CI: −1.87 to - 0.16).

Comparison of Saffron with Fluoxetine

Figure 2 shows the efficacy of Saffron compared to Fluoxetine. Heterogeneity observed among studies was 15% (as such, a fixed model was used). The SMD was found to be 0.11 (95% CI: −0.20 to 0.43). When stratifying according to the doses (20 and 40 mg), SMDs were computed 0.33 (95% CI: −0.30 to 0.95) and 0.06 (95% CI: −0.34 to 0.46), respectively.

Sensitivity analysis

The impact of each study on the overall outcome was evaluated performing sensitivity analysis. To ensure the stability of the results, we conducted a sensitivity analysis (Figure S3 and S4). In both sensitivity analyses, the results did not statistically change, confirming the stability of the findings.

Discussion

Depression is a commonly diagnosed psychiatric disorder that can dramatically impact on quality of life.[30] For the treatment of this disease, various drugs can be used, even though they can have different side-effects. Concerning safety, herbal medicines, such as saffron, can represent a valid alternative.[22,31,32] Saffron can also be used to relieve menopausal symptoms and to treat other disorders, such as cancer and metabolic syndrome.[33]

This systematic review and meta-analysis were conducted to evaluate the effectiveness of saffron versus placebo and Fluoxetine 20or 40 mg in treating patients with depression. The findings of this study showed that saffron administration was well comparable with Fluoxetine.

Table 1 Main characteristics of studies included in the present systematic review and meta-analysis

Study	Year	Country	Sex		Drugs		Duration
			Female	Male	Experimental	Control	
Akhondzadeh et al[22]	2005	Iran	18	22	Saffron	Placebo	6 weeks
Moshiri et al[24]	2006	Iran	17	23	Saffron	Placebo	6 weeks
Akhondzadeh Basti et al[26]	2008	Iran	22	22	Saffron	Placebo	6 weeks
Mazidi et al[28]	2016	Iran	30	30	Saffron	Placebo	12 weeks
Noorbala et al[23]	2005	Iran	20	20	Saffron 30 mg	Fluoxetine 40 mg	6 weeks
Akhondzadeh Basti et al[25]	2007	Iran	21	19	Saffron 30 mg	Fluoxetine 20 mg	8 weeks
Shahmansouri et al[27]	2014	Iran	25	15	Saffron 30 mg	Fluoxetine 40 mg	6 weeks
Kashani et al[29]	2016	Iran	64	-	Saffron 30 mg	Fluoxetine 40 mg	6 weeks

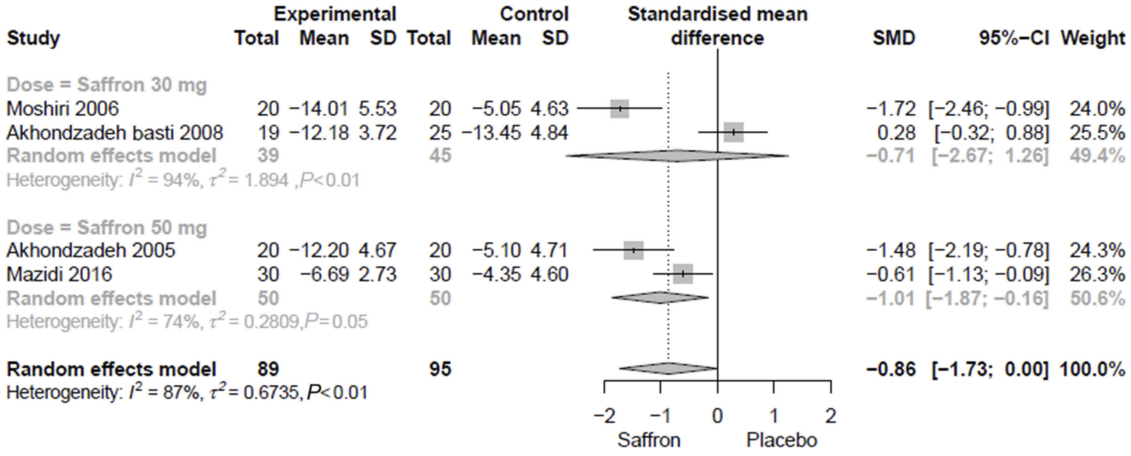

Figure 1 The overall SMD of Saffron compared to placebo.

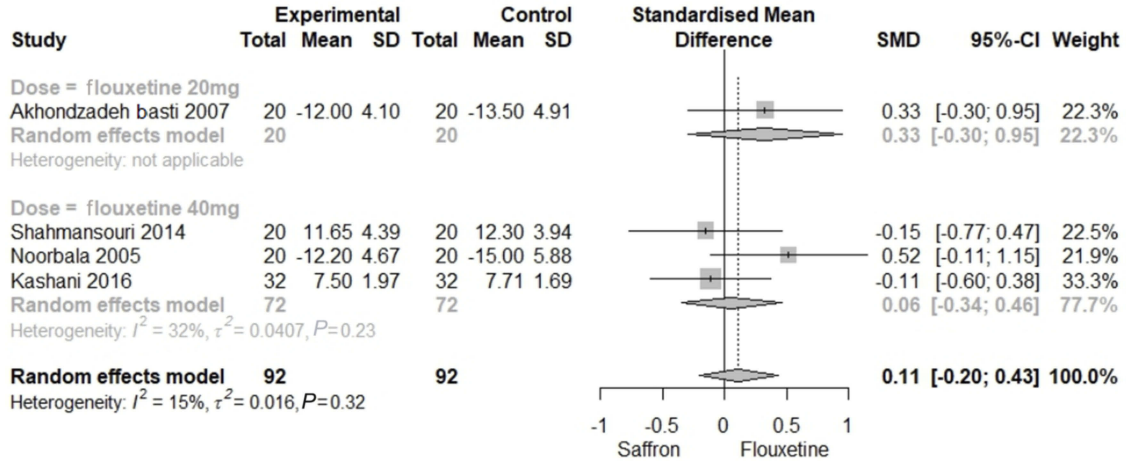

Figure 2 The overall SMD of Saffron compared to Fluoxetine.

From a biochemical standpoint, in depressed patients, saffron seems to finely tune the level of some neurotransmitters, for example, increasing serotonin levels, inhibiting serotonin reuptake in synapses.[34,35] Besides its serotoninergic activity, saffron also modulates hypothalamus-pituitary-adrenal (HPA) axis and exerts neuroprotective effects. Indeed, saffron can increase the concentrations of superoxide dismutase, catalase, and glutathione peroxidase, while lowering malondialdehyde levels and inhibiting the lipid peroxidation pathway. Moreover, saffron positively influences neuronal plasticity and neurogenesis of various brain regions, such as hippocampus, nucleus accumbens, and prefrontal cortex, among others.

Saffron contains more than 150 volatile and nonvolatile, aroma-yielding chemical compounds such as vitamins (like thiamine and riboflavin), amino acids, peptides and proteins, minerals and polysaccharides. Furthermore, saffron contains flavonoids and carotenoids, including zeaxanthin, lycopene, beta-carotenes, crocins (a family of six mono- or di-glycosyl polyene esters, derivatives of 8′-diapocarotene -8,8′- dioic acid, a hydrophilic carotenoid), crocetin (8,8′-diapo-8,8′-carotenoic acid, a carotenoid dicarboxylic acid precursor of crocin), safranal, picrocrocin (4-(β-D-glucopyranosyloxy)-2,6,6-trimethyl-1-cyclohexene-1-carboxaldehyde, a molecule derived from the degradation of zeaxanthin and a monoterpene glycoside precursor of safranal) and other substances that have antioxidant properties, thus potentially playing an important role in protecting against free radicals, anti-inflammatory and reactive molecules.[28,36] Some studies have shown that the consumption of saffron can result into an improvement of the Hamilton Depression Rating Scale (HDRS) score. Some studies carried out in animal models of depression, such

as the study of Hosseinzadeh et al[37] have examined the effectiveness of saffron in reducing depressive symptoms.

The findings of this study showed that saffron consumption has similar results with the administration of Fluoxetine, a drug commonly prescribed for the treatment of depression. This seems to suggest that the use of saffron in treating depressed patients can be effective as well, representing a suitable and safer alternative to Fluoxetine. In another study, saffron and Imipramine were used for depressed patients and compared. Results showed that saffron improved the symptoms of the patients in a comparable way to Imipramine.[32]

To the best of our knowledge, this study was the most comprehensive study on the effectiveness of saffron compared to placebo and Fluoxetine in patients with depression, with respect to previous systematic reviews and meta-analyses,[38,39,40,41] specifically focusing on an antidepressant (fluoxetine), for more consistency and accuracy of the findings, instead of pooling together different antidepressants. Furthermore, we have performed a comprehensive literature search in validated databases, sensitivity analyses, and sub-group analyses. These represent the main strengths of this study.

Limitations

However, there are some limitations in the current systematic review and meta-analysis that should be properly recognized:

1. The number of studies that have assessed the effectiveness of saffron in treating depressed patients is low. More clinical trials are needed to better evaluate the efficacy of this plant.
2. Given the highly statistically significant heterogeneity among studies, random-effect models were used and preferred to fixed-effect models. To further minimize the heterogeneity, sub-group analyses stratified according to the dosage of drugs used were carried out.
3. Due to the small number of included studies, it was not possible to check the existence of publication bias.
4. All studies have been done in Iran, which accounts for 90% of saffron production, on Iranian patients. Since ethnic differences can impact on drugs efficacy, studies in other countries seem necessary.
5. The duration of the studies included varied between 6 and 12 weeks. Studies conducted over a longer period of time to assess the efficacy of the drug at longer intervals are, therefore, needed.

Conclusions

The findings of the present systematic review and meta-analysis showed that the use of saffron improved the symptoms of depressed patients. However, on the basis of the abovementioned shortcomings, to ensure the effectiveness of this compound in treating depression, further high-quality studies are needed to provide more solid and valuable evidence.

Abbreviations list

WHO, World Health Organization; DALY, disability-adjusted life year; PRISMA, preferred reporting items for systematic reviews and meta-analyses; RCT, randomized clinical trial; SMD, standardized mean differences; CI, confidence interval.

Acknowledgment

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Disclosure

The authors declare that they have no competing interests in this work.

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Supplementary materials

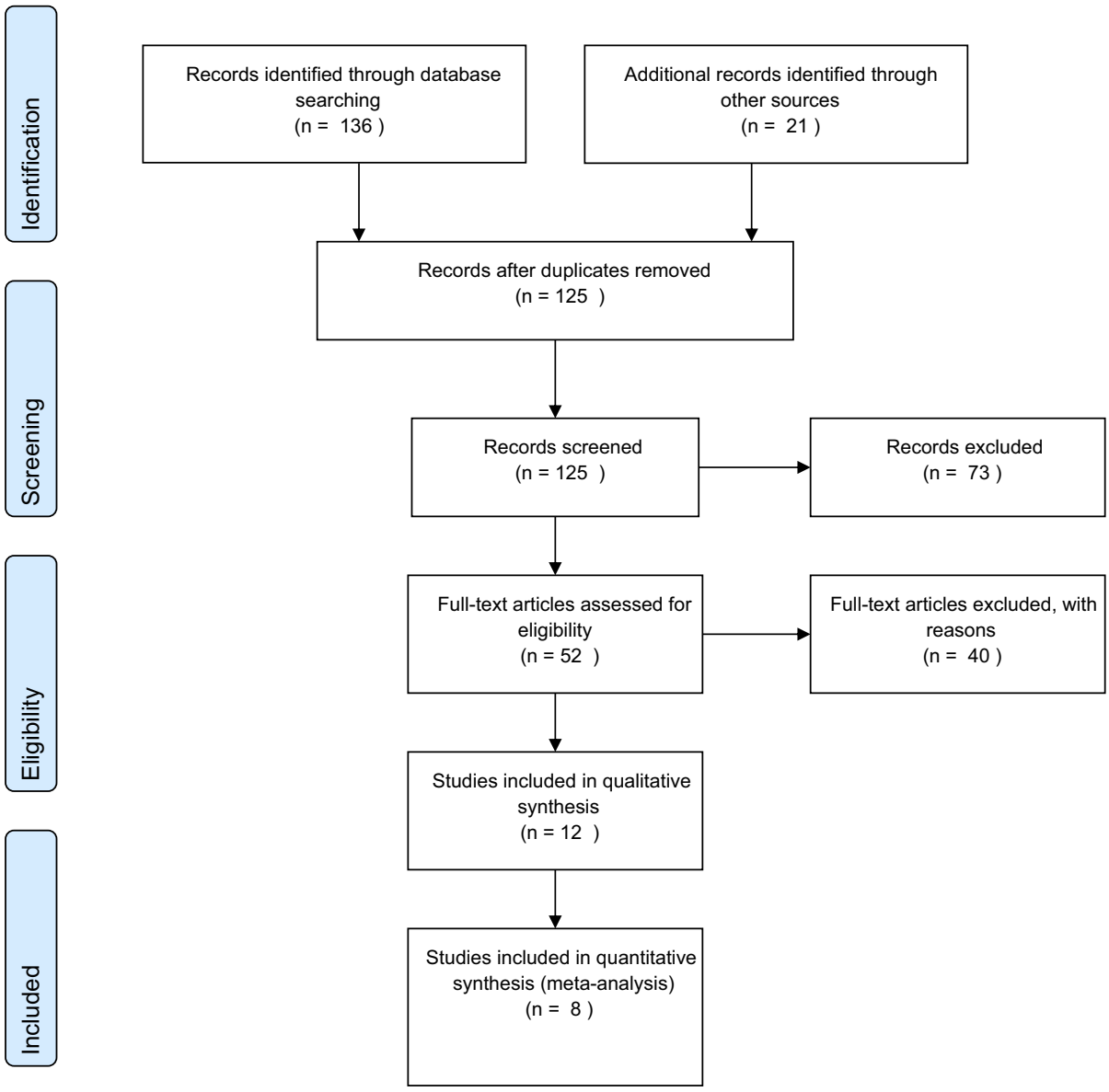
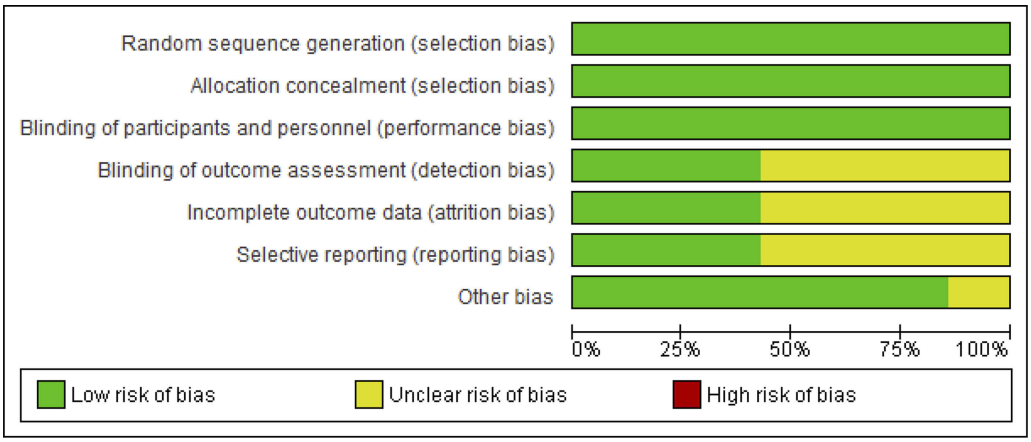


Figure S1 The flow-chart of the current systematic review and meta-analysis.



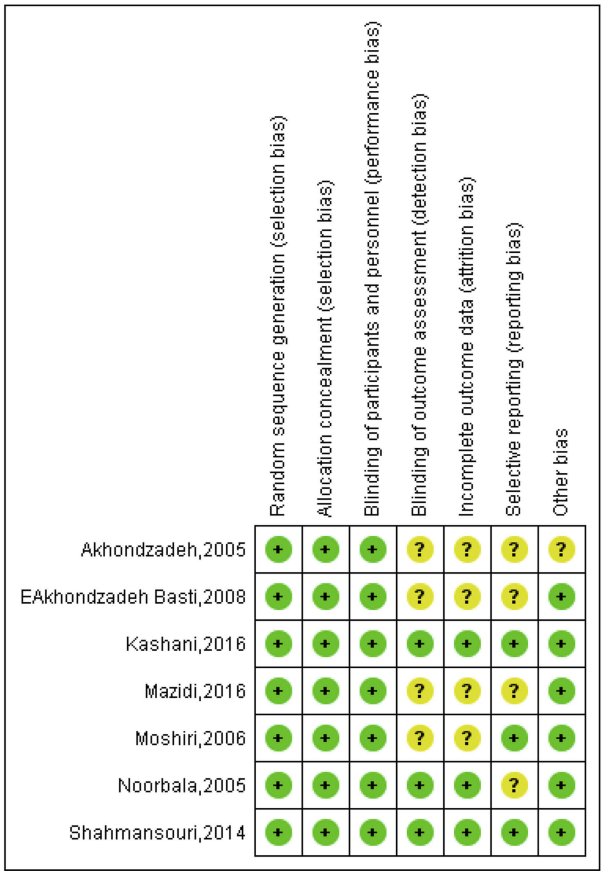


Figure S2 The risk of bias assessment of studies included.

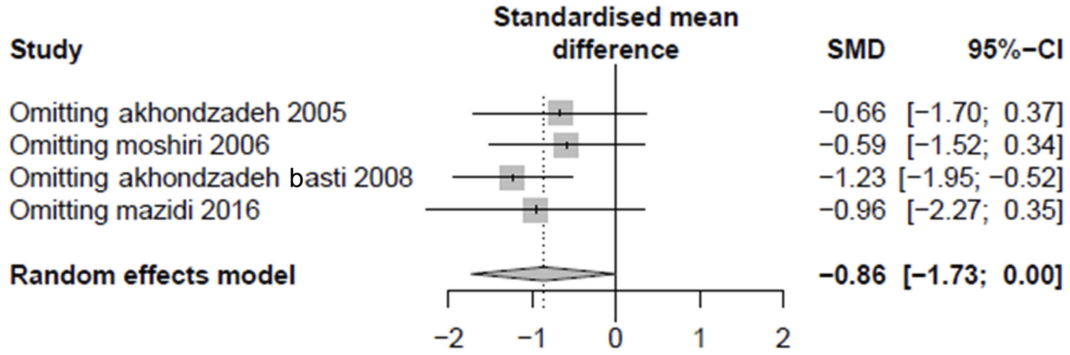


Figure S3 The sensitivity analysis of Saffron compared to placebo.

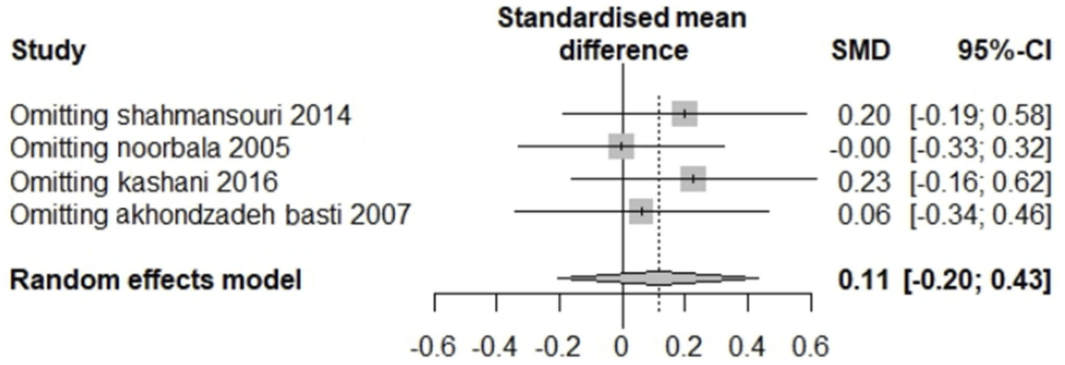


Figure S4 The sensitivity analysis of Saffron compared to fluoxetine.