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

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

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## 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.

## 1 2 Introduction

2 Saffron (*Crocus sativus L.*) and its constituents including, crocin, crocetin, and safranal may  
3 have a positive effect on several neurobiological mechanisms implicated in mental illness <sup>1-3</sup>.  
4 In animal models, whole saffron and implicated compounds have been reported to modulate  
5 pathways related to neurotransmitters, immune regulation, inflammation, oxidative stress,  
6 hypothalamus-pituitary-adrenal (HPA) axis, and neurotrophins <sup>4</sup>. For example, in rats, the  
7 administration of a saffron extract dose-dependently increased brain concentrations of  
8 dopamine and, at high doses, increased glutamate levels <sup>5</sup>. In another study, the  
9 administration of crocin modulated serotonergic activity in rats exposed to the non-selective  
10 serotonin receptor agonist meta-chlorophenylpiperazine, lowering obsessive-like behaviours  
11 <sup>6</sup>. Saffron constituents also have anti-inflammatory, immune regulating, and antioxidant  
12 properties, including the modulation of endogenous antioxidant enzymes <sup>7-11</sup>. In addition,  
13 studies using animal stress models have confirmed that saffron modulates HPA axis activity  
14 by reducing plasma corticosterone concentrations <sup>12,13</sup>. Finally, support for the  
15 neuroprotective effects of saffron and its constituent, crocin, is derived from studies  
16 demonstrating positive effects on the neurotrophin, brain-derived neurotrophic factor (BDNF)  
17 in animal stress models <sup>14,15</sup>.

18 Two previous meta-analyses have reported saffron supplementation to improve measures of  
19 depression in clinical trials <sup>16,17</sup>. Previous meta-analyses on this topic, however, have only  
20 examined effects of saffron on depression in clinical populations with mild to major  
21 depression <sup>16,17</sup>. Furthermore, since the publication of these reviews, several published  
22 intervention studies have been conducted both in depression and in other mental illnesses.  
23 Therefore, using the Preferred Reporting Items for Systematic Reviews and Meta-analyses  
24 (PRISMA) guidelines, this systematic review and meta-analysis of randomized, controlled

25 trials (RCTs) aims to examine the transdiagnostic effects of saffron supplementation (as a  
26 stand-alone or adjunctive intervention) on symptoms of mental illness in both clinical and  
27 general populations compared with pharmacotherapy or placebo.

28

## 29 **3 Methods**

### 30 **3.1 Literature search**

31 This review was written in accordance with the PRISMA (Supplementary Material 1)<sup>18</sup> and  
32 was prospectively registered on PROSPERO (CRD42017070060). A search strategy was  
33 developed based on the research question (Table 1). Studies were identified using the  
34 following databases: Medline (Pubmed), PsychInfo, Embase, The Cochrane Library, and  
35 CINAHL. Search terms were related to saffron and its constituents (“saffron” OR “crocus”  
36 OR “crocin” OR “croctin”) and mental health outcomes (“depression” OR “depressive  
37 disorder” OR “anxiety disorders” OR “affective symptoms” OR *anxi\** OR mood OR  
38 “psychological symptoms” OR “psychological distress”). The search strategy identified  
39 articles published since journal inception up to March 2018.

40 Studies were required to be RCTs including cross-over studies; published in English,  
41 included measures of mental health (e.g. depression, low mood, depressive symptoms,  
42 emotional problems, and anxiety), and used any component of saffron (e.g. whole saffron,  
43 standardized extracts, parts of saffron or specific saffron-derived compounds). Interventions  
44 that included saffron in combination with standard medications were included; however,  
45 combined interventions with other novel ingredients were excluded. No limit on age or  
46 population was included and the comparator could be either placebo or pharmacotherapy.

### 47 3.2 *Data extraction*

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

### 56 3.3 *Assessment of study risk of bias*

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

### 60 3.4 *Statistical Analyses*

61 The meta-analyses were conducted in Comprehensive Meta-Analysis 3.0<sup>20</sup> using a  
62 DerSimonian-Laird random-effects model<sup>21</sup> to account for heterogeneity between studies.  
63 The primary outcome was the effect of saffron on total depressive symptoms in comparison  
64 to placebo control conditions. The effect of saffron on symptoms of depression as an  
65 adjunctive to medication and as a stand-alone intervention compared to medication was also  
66 computed as a secondary outcome. The effect of saffron on symptoms of anxiety compared to  
67 placebo, medication and as an adjunctive intervention were also computed when sufficient  
68 data were available. Mean change scores in symptoms for saffron and control conditions were  
69 compared using random-effects meta-analyses to compute effect size of saffron compared to

70 control condition as Hedges'  $g$  (with 95% confidence intervals (CI)). For studies that used  
71 more than one measure of the same outcome, the measure identified as the primary outcome  
72 by the respective study was used in meta-analyses. Otherwise, an average change score  
73 across all measures was computed and used in the pooled analysis. In multi-arm trials that  
74 had more than one active saffron condition, a pooled effect was computed across all saffron  
75 arms compared to the non-saffron comparator conditions. To examine the possibility of  
76 publication bias affecting results, Eggers'  $t$ -test was conducted. Finally, to further account for  
77 the potential impact of publication bias, a Duval and Tweedie's trim-and-fill analysis was  
78 applied to in order to recalculate effect sizes after statistically accounting for outlier studies.  
79 Additionally, subgroup analyses were conducted to examine the (i) effects of saffron in  
80 comparison to antidepressant medications, and (ii) the effect of saffron on depression when  
81 used as an adjunctive treatment alongside antidepressants (i.e. studies comparing saffron to  
82 placebo in samples already taking, or commencing, antidepressant medications).  
83 Heterogeneity between studies was examined using Cochran's  $Q$  (with  $p$ -value) and  $I^2$   
84 estimates. These statistics estimate the extent to which statistical heterogeneity between  
85 studies has arisen from genuine inter-study differences, rather than due to chance.

## 86 **4 Results**

### 87 **4.1 Study selection**

88 As represented in Figure 1, the search strategy resulted in 310 de-duplicated studies that were  
89 screened to identify 23 eligible studies for inclusion (see Table 2).

### 90 **4.2 Study Characteristics**

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



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

#### 104 **4.3 Interventions**

105 Most studies (19/23) used a dose of 30 mg per day of saffron. Ten studies used the stigma of  
106 saffron, 4 studies used saffron petals, 3 used crocin only, and the remaining studies used  
107 either a whole powder or did not provide further details. Nine studies reported that the  
108 intervention was standardized to contain either crocin, safranal, or lepticrosalides<sup>®</sup> (a measure  
109 of bioactive compounds present in saffron, including safranal and crocin isomers).

#### 110 **4.4 Outcome measures**

111 Depressive symptoms (22/23) were more commonly investigated than anxiety symptoms  
112 (8/23). Depression and/or anxiety symptoms were measured using either the Hamilton Rating  
113 Scale for Depression or Anxiety, Beck Depression Inventory, Depression Anxiety Stress  
114 Scale (DASS) 21, or Revised Child Anxiety and Depression Scale (RCADS; youth and  
115 parent versions). One study assessed mood using the Profile of Mood States (POMS) and  
116 Positive and Negative Affect Schedule (PANAS) 21 tools.

## 117 4.5 Study Results

### 118 4.5.1 Effects of Saffron on Depressive Symptoms

119 Random-effects meta-analysis found a significant and large positive effect size for saffron  
120 reducing symptoms of depression in comparison to placebo ( $g=0.99$ , 95% CI=0.61 to 1.37,  
121  $n=14$  studies,  $n=716$  participants,  $p<0.001$ ; Figure 2). An additional study that could not be  
122 entered into the meta-analysis due to insufficient available data also reported saffron to  
123 significantly improve depressive symptoms compared to placebo<sup>30</sup>. There was significant  
124 heterogeneity across the study data ( $Q=71.8$ ,  $p<0.001$ ,  $I^2=81.9\%$ ). Egger's regression test  
125 found strong evidence of publication bias (Intercept= $6.99$ ,  $p=0.007$ ). The funnel plot of  
126 publication bias is displayed in Supplementary Material 3. Correcting for publication bias  
127 using a trim-and-fill analysis increased the effect size of saffron supplementation ( $g=1.14$ ,  
128 95% CI=0.74 to 1.52).

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

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

140 depressive symptoms between the adjunctive group (fluoxetine and saffron) and control  
141 (fluoxetine and placebo) <sup>31</sup>.

#### 142 4.5.2 *Effects of Saffron on Symptoms of Anxiety*

143 Figure 3 displays the effects of saffron mono and adjunctive therapy on symptoms of anxiety  
144 across 6 RCTs compared to placebo (n=375 participants). Random-effects meta-analysis  
145 found a large positive effect size for saffron on reducing symptoms of anxiety in comparison  
146 to placebo control conditions (g=0.95, 95% CI=0.27 to 1.63,  $p<0.006$ ). There was significant  
147 heterogeneity across the study data (Q=44.38,  $p<0.001$ ,  $I^2=88.74%$ ). Egger's regression test  
148 found strong evidence of publication bias (Intercept=0.12,  $p=0.028$ ). Correcting for  
149 publication bias using a trim-and-fill analysis increased the effect size of saffron  
150 supplementation (g=1.40, 95% CI=0.60 to 2.150). There were insufficient studies to conduct  
151 a meta-analysis of the effect of saffron on anxiety in comparison to antidepressant  
152 medications or to conduct subgroup analysis of saffron as an adjunctive treatment. One study  
153 that investigated the effect of saffron for anxiety symptoms compared to citalopram reported  
154 no significant difference between treatment groups <sup>27</sup>.

#### 155 4.5.3 *Sensitivity Analyses*

156 Sensitivity analyses were performed to exclude one outlier study that could be influencing the  
157 overall findings <sup>32</sup>. Exclusion of this study only slightly reduced the overall effect size of  
158 saffron on depressive symptoms compared to placebo (g=0.84, 95% CI=0.53 to 1.16,  
159  $p<0.001$ ), although large heterogeneity (Q=45.45,  $p<0.001$ ,  $I^2=73.8%$ ) and significant  
160 publication bias was still evident in the remaining 13 studies (Eggers regression intercept =  
161 4.957,  $p=0.043$ ).

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

164 results remained the same ( $g=0.48$ , 95% CI=0.25 to 0.70,  $p<0.001$ ). There was also little  
165 indication of heterogeneity ( $Q=3.39$ ,  $p=0.50$ ,  $I^2=0\%$ ) or publication bias (Eggers regression  
166 intercept = 0.23,  $p=0.47$ ) in the remaining 5 studies, although this is likely due to standard  
167 tests for detecting heterogeneity/publication bias in meta-analysis being underpowered in this  
168 small a number of studies.

#### 169 4.5.4 *Effects of Saffron on Additional Outcomes*

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

#### 179 4.6 *Adverse events*

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

## 184 5 Discussion

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

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

190 The results of this meta-analysis are consistent with two prior meta-analyses that investigated  
191 saffron for mild-to-major depression only<sup>16,17</sup>. Saffron had a significant large positive effect  
192 size when compared to placebo for both depression and anxiety outcomes. For depressive  
193 outcomes, saffron also had a significant large positive effect size when used as an adjunctive  
194 treatment to antidepressants and when compared against antidepressant medications, there  
195 was no significant difference between groups. The included studies demonstrate that saffron  
196 supplementation appears to be well-tolerated with few adverse events being reported within  
197 the included studies or by other authors<sup>34</sup>. However, all studies to date have been of  
198 relatively short duration and with a limited sample size. Therefore, longer-term trials that are  
199 suitably powered are required to assess the safety of saffron supplementation.

200 In the context of standard interventions for depression and anxiety, the results from the  
201 placebo-controlled trials, suggest an effect size that is considerably greater than standard  
202 pharmacotherapy, such as selective serotonin reuptake inhibitors (Cohen's  $d=0.30$ )<sup>35</sup>.  
203 However, the five trials directly comparing saffron to antidepressant medication reported no  
204 statistically significant difference ( $p=0.33$ ). Due to the large effect sizes, the significant  
205 publication bias detected for both outcomes, and the majority of trials being conducted in one  
206 region, many by the same research group (13/23), there is a need to replicate these results  
207 within other populations and in large, well-powered, rigorous trials before clinical  
208 recommendations are justified. Similarly, greater rigour regarding Good Manufacturing  
209 Practice and standardization, dosage and characterization of the active ingredients is needed.

210 In addition to the need to replicate existing studies, there are additional areas recommended  
211 for future studies. First, the use of saffron for other mental illnesses is currently  
212 underexplored. While seven studies assessed anxiety symptoms, only one study included  
213 participants with a diagnosed anxiety disorder. Similarly, one study evaluated the safety and  
214 feasibility of saffron in schizophrenia, but no efficacy trials have been conducted to date <sup>36</sup>.  
215 Furthermore, there is a need to explore comparative efficacy of the different components of  
216 saffron. One study reported that saffron petal and stigma had equivalent efficacy in treating  
217 depressive symptoms in participants with major depression but there is insufficient literature  
218 to comment on particular components at this stage <sup>37</sup>. Due to the high cost of saffron for  
219 culinary use, previous reviews have recommended the investigation of the efficacy of less  
220 expensive parts of saffron (e.g. petal and corm) <sup>4</sup>. However, due to the small therapeutic  
221 dosage used in current studies, the cost of saffron formulations is unlikely to be considerably  
222 higher than for other nutraceutical interventions.

223 Preclinical studies suggest that compounds contained within saffron have a range of  
224 potentially relevant mechanisms of action including antioxidant, anti-inflammatory properties  
225 and are able to modulate BDNF expression and the HPA-axis <sup>4</sup>. However, these pathways  
226 have been largely unexplored within clinical trials. Hence, there is a need to measure markers  
227 of relevant pathways within future clinical trials to explore the association between changes  
228 of these biological markers and clinical symptoms. Furthermore, as demonstrated by  
229 Rapaport et al.<sup>38</sup>, who reported that treatment response to omega-3 (eicosapentaenoic acid)  
230 was greater in those with higher inflammation at baseline, measuring relevant biomarkers  
231 may provide valuable information regarding specific populations and participant stratification  
232 to determine who is likely to respond to saffron treatment. Related to this is the need for  
233 dose-finding studies to establish the optimal dosing regimen. Most studies have used 30mg

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

## 236 **6 Conclusion**

237 In summary, the existing evidence suggests a potential for saffron to be an efficacious  
238 intervention for symptoms of depression and anxiety. However, the strength of this  
239 conclusion is moderated by the lack of large-scale trials, and significant risk of publication  
240 bias among the many small- scale pilot trials published on this topic. Indeed, the large effect  
241 sizes reported in some studies require replication in further clinical trials that address  
242 methodological limitations and the lack of regional diversity before clinical recommendations  
243 can be made. Trials that explore the mechanisms of action of saffron, dosage, active  
244 ingredients, long-term safety, as well as the efficacy in diagnosed mental illnesses are also  
245 required.

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## 270 **Author Contributions**

271 All authors contributed to final manuscript. WM led all stages of the manuscript. ML and AL  
272 conducted the data extraction. SM conduct the risk of bias assessment. TR, ML and AR  
273 extracted the data from included studies. ALopresti contributed to the mechanisms discussion  
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275



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

	<p><b>Country:</b> Iran</p> <p><b>Sample size:</b> 40 enrolled, 38 completed</p> <p><b>Total study period:</b> 8 weeks</p>	<p>depression based on the SCID-IV</p> <p><b>Age in years (average):</b> 34</p>		<p><b>Outcomes measured at:</b> Baseline, week 1, week 2, week 4, week 6 and week 8 (endpoint)</p>	<p>baseline to endpoint (<math>P &lt; 0.001</math>). No significant difference at endpoint between the two groups (<math>P = 0.84</math>).</p>
Akhondzadeh et al. (2005) <sup>39</sup>	<p><b>Study design:</b> Randomized, double blind, parallel group</p> <p><b>Country:</b> Iran</p> <p><b>Sample size:</b> 40 enrolled, 35 completed</p> <p><b>Total study period:</b> 6 weeks</p>	<p>Male and female outpatients who met DSM-IV criteria for major depression based on the SCID-IV</p> <p><b>Age in years (average):</b> 36</p>	<p>30 mg Saffron (stigma) OR Placebo</p>	<p><b>Outcomes measured:</b> Depression measured using HAM-D-17</p> <p><b>Outcomes measured at:</b> Baseline, week 1, week 2, week 4 and week 6 (endpoint)</p>	<p>The HAM-D-17 score significantly decreased in both the Saffron and Placebo groups from baseline to endpoint (<math>P &lt; 0.001</math>). However, the Saffron group had significantly lower HAM-D-17 scores at endpoint compared to Placebo (<math>P &lt; 0.001</math>).</p>



Akhondzadeh et al. (2004) <sup>26</sup>	<p><b>Study design:</b> Randomized, double blind, parallel group</p> <p><b>Country:</b> Iran</p> <p><b>Sample size:</b> 30 enrolled, 30 completed</p> <p><b>Total study period:</b> 6 weeks</p>	<p>Male and female outpatients who met DSM-IV criteria for major depression based on the SCID-IV</p> <p><b>Age in years (average):</b> 34</p>	<p>30 mg Saffron (stigma) OR 100 mg Imipramine</p>	<p><b>Outcomes measured:</b> Depression measured using HAM-D-17</p> <p><b>Outcomes measured at:</b> Baseline, week 1, week 2, week 3, week 4, week 5 and week 6 (endpoint)</p>	<p>The HAM-D-17 score significantly decreased in both the Saffron and Imipramine groups from baseline to endpoint (<math>P &lt; 0.001</math>). No significant difference at endpoint between the two groups (<math>P = 0.09</math>).</p>
Agha-Hosseini et al. (2008) <sup>40</sup>	<p><b>Study design:</b> Randomized, double blind, placebo controlled</p> <p><b>Country:</b> Iran</p> <p><b>Sample size:</b> 50 enrolled, 47 completed</p>	<p>Women with regular menstrual cycles and experience of PMS symptoms for at least 6 months</p> <p><b>Age in years (average):</b> 34</p>	<p>30 mg Saffron (petal) OR Placebo</p>	<p><b>Outcomes measured:</b> Depression measured using HAM-D-17</p> <p>PMS factors including mood (e.g. anxiety, irritability, depression, nervous tension, mood</p>	<p>The HAM-D-17 score significantly decreased in the Saffron group compared to Placebo from baseline to endpoint (<math>P &lt; 0.001</math>).</p> <p>The total Daily Symptom Report Checklist score significantly decreased in</p>

	<b>Total study period:</b> 8 weeks; or two menstrual cycles (cycles 3 and 4)			swings and out of control) measured using Daily Symptom Report Checklist  <b>Outcomes measured at:</b> 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) <sup>27</sup>	<b>Study design:</b> Randomized, double blind, parallel group  <b>Country:</b> 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	<b>Outcomes measured:</b> 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

	<p><b>Sample size:</b> 66 enrolled, 60 completed</p> <p><b>Total study period:</b> 6 weeks</p>	<p><b>Age in years (average):</b> 36</p>		<p>Anxiety measured using HAM-A</p> <p><b>Outcomes measured at:</b> Baseline, week 2, week 4 and week 6 (endpoint)</p>	<p>endpoint (<math>P &lt; 0.001</math>). No significant difference for either HAM-D-17 or HAM-A scores at endpoint between the two groups (<math>P = 0.715</math> and <math>P = 0.999</math>, respectively).</p>
Jafarnia et al. (2017) <sup>41</sup>	<p><b>Study design:</b> Randomized, double blind, placebo controlled</p> <p><b>Country:</b> Iran</p> <p><b>Sample size:</b> 40 enrolled, 40 completed</p> <p><b>Total study period:</b> 6 weeks</p>	<p>Male and female patients who met DSM-IV criteria for mild-to-moderate Generalised Anxiety Disorder (GAD) and were receiving Sertraline</p> <p><b>Age in years (average):</b> 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><b>Outcomes measured:</b> Anxiety measured using HAM-A</p> <p><b>Outcomes measured at:</b> Baseline, week 3 and week 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 (<math>P &lt; 0.000</math>). However, the Saffron (coupled with Sertraline) group had significantly lower HAM-A</p>

					scores at endpoint compared to Placebo (coupled with Sertraline), ( $P < 0.005$ ).
Jam et al. (2017) <sup>42</sup>	<p><b>Study design:</b></p> <p>Randomized, double blind, placebo controlled</p> <p><b>Country:</b> Iran</p> <p><b>Sample size:</b> 34 enrolled, 33 completed</p> <p><b>Total study period:</b> 8 weeks</p>	<p>Male and female patients with Metabolic Syndrome (MetS) and depressive symptoms based on the BDI</p> <p><b>Age in years (average):</b> 46</p>	<p>30 mg Saffron (crocin) OR Placebo</p>	<p><b>Outcomes measured:</b></p> <p>Depression measured using BDI</p> <p><b>Outcomes measured at:</b></p> <p>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 (<math>P &lt; 0.005</math> and <math>P &gt; 0.05</math>, respectively). Significant difference at endpoint between the two groups (<math>P = 0.013</math>).</p>
Jelodar et al. (2018) <sup>43</sup>	<p><b>Study design:</b></p> <p>Randomized, double blind, placebo controlled</p> <p><b>Country:</b> Iran</p>	<p>Male and female outpatients who met DSM-IV criteria for major</p>	<p>30 mg Saffron (stigma) AND 20 mg Fluoxetine OR Placebo AND 20 mg Fluoxetine</p>	<p><b>Outcomes measured:</b></p> <p>Depression measured using BDI</p>	<p>The BDI score significantly decreased in both the Saffron (coupled with Fluoxetine) and Placebo</p>

	<p><b>Sample size:</b> 40 enrolled, 40 completed</p> <p><b>Total study period:</b> 4 weeks</p>	<p>depression based on the SCID-IV</p> <p><b>Age in years (range):</b> 20 to 55</p>		<p><b>Outcomes measured at:</b> Baseline and week 4 (endpoint)</p>	<p>(coupled with Fluoxetine) groups from baseline to endpoint (<math>P &lt; 0.05</math>). No significant difference at endpoint between the two groups (<math>P &lt; 0.056</math>).</p>
<p>Kashani et al. (2018)<sup>44</sup></p>	<p><b>Study design:</b> Randomized, double blind, placebo controlled</p> <p><b>Country:</b> Iran</p> <p><b>Sample size:</b> 60 enrolled, 56 completed</p> <p><b>Total study period:</b> 6 weeks</p>	<p>Women who met DSM-IV criteria for major depression and mild-to-moderate depression based on HDRS as well as post-menopausal hot flashes</p> <p><b>Age in years (average):</b> 55</p>	<p>30 mg Saffron (stigma) OR Placebo</p>	<p><b>Outcomes measured:</b> Depression measured using HDRS</p> <p><b>Outcomes measured at:</b> Baseline, week 2, week 4 and week 6 (endpoint)</p>	<p>The HDRS score significantly decreased in both Saffron and Placebo groups from baseline to endpoint (<math>P &lt; 0.01</math>). However, the Saffron group had significantly lower HDRS scores at endpoint compared to Placebo (<math>P &lt; 0.001</math>).</p>

Kashani et al. (2017) <sup>23</sup>	<p><b>Study design:</b> Randomized, double blind, parallel group</p> <p><b>Country:</b> Iran</p> <p><b>Sample size:</b> 68 enrolled, 64 completed</p> <p><b>Total study period:</b> 6 weeks</p>	<p>Women who met DSM-IV criteria for post-partum depression 4-12 weeks after childbirth as well as scoring &gt; 10 and &lt; 18 on HDRS</p> <p><b>Age in years (average):</b> 30</p>	<p>30 mg Saffron (stigma) OR 20 mg Fluoxetine</p>	<p><b>Outcomes measured:</b> Depression measured using HDRS</p> <p><b>Outcomes measured at:</b> Baseline, week 1, week 3 and week 6 (endpoint)</p>	<p>*Significance 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 two groups (<math>P = 0.37</math>).</p>
Kashani et al. (2013) <sup>45</sup>	<p><b>Study design:</b> Randomized, double blind, placebo controlled</p> <p><b>Country:</b> Iran</p> <p><b>Sample size:</b> 38 enrolled, 34 completed</p>	<p>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%</p>	<p>30 mg Saffron (petal) AND 40 mg Fluoxetine OR Placebo AND 40 mg Fluoxetine</p>	<p><b>Outcomes measured:</b> Depression measured using HDRS</p> <p><b>Outcomes measured at:</b> Baseline, week 2 and week 4 (endpoint)</p>	<p>*Significance of reduction in HDRS score within groups for Saffron (coupled with Fluoxetine) and Placebo (coupled with Fluoxetine) from baseline to endpoint not recorded.</p>

	<b>Total study period:</b> 4 weeks	reduction in depression score)  <b>Age in years (average):</b> 35			No significant difference at endpoint between the two groups ( $P = 0.278$ ).
Kell et al. (2017) <sup>28</sup>	<b>Study design:</b> Randomized, double blind, parallel group, placebo controlled  <b>Country:</b> Australia  <b>Sample size:</b> 128 enrolled, 121 completed  <b>Total study period:</b> 4 weeks	Male and females self-reporting low mood but not diagnosed with depression or another mood disorder and who were otherwise healthy  <b>Age in years (average):</b> 39	28 mg Saffron (stigma) OR Saffron 22 mg (stigma) Saffron OR Placebo	<b>Outcomes measured:</b> 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  <b>Outcomes measured at:</b> 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

					<p>groups regarding (<math>P = 0.124</math>). However, the PANAS-21 score for Negative Affect significantly decreased for the 28 mg Saffron group compared to Placebo at endpoint (<math>P &lt; 0.001</math>).</p> <p>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 (<math>P &lt; 0.001</math> and <math>P = 0.001</math>, respectively). No significant difference at endpoint between the 22 mg</p>
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				<p>Saffron and Placebo groups (<math>P = 0.449</math>).</p> <p>The DASS-21 score for anxiety significantly decreased for the 28 mg Saffron group compared to Placebo at endpoint (<math>P &lt; 0.010</math>). No significant difference between 22 mg Saffron group compared to 28 mg Saffron or Placebo groups at end point (<math>P = 0.149</math> and <math>P = 0.625</math>, respectively).</p> <p>The DASS-21 score for stress significantly decreased for the 28 mg Saffron group compared to</p>
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					both the 22 mg Saffron and Placebo groups at endpoint ( $P < 0.001$ and $P = 0.001$ , respectively).
Lopresti et al. (2018) <sup>29</sup>	<p><b>Study design:</b> Randomized, double blind, placebo controlled</p> <p><b>Country:</b> Australia</p> <p><b>Sample size:</b> 80 enrolled, 68 completed</p> <p><b>Total study period:</b> 8 weeks</p>	Male and female youth who were assessed as suffering from mild-to-moderate anxiety and depressive symptoms	14 mg Saffron (stigma) OR Placebo	<p><b>Outcomes measured:</b> Depression and anxiety measured using youth and parent reports for RCADS, Revised Child Anxiety and Depression Scale.</p> <p>Subscales: separation anxiety; generalised anxiety; panic; social phobia; obsessions/compulsions; depression</p>	<p><b>Youth reports:</b> The total RCADS score significantly decreased from baseline to endpoint for the Saffron group compared to Placebo (<math>P &lt; 0.049</math>), and three subscale scores: separation anxiety (<math>P = 0.003</math>); social phobia (<math>P = 0.023</math>); and, depression (<math>P = 0.016</math>).</p> <p><b>Parent reports:</b> No significant difference from baseline to endpoint for total RCADS scores</p>

				<p><b>Outcomes measured at:</b></p> <p>Baseline, week 2, week 4, week 6 and week 8 (endpoint)</p>	<p>between groups (<math>P = 0.749</math>). Saffron had a significant mean improvement (<math>P = 0.026</math>), and in two subscales from baseline to endpoint: generalised anxiety (<math>P &lt; 0.01</math>); and, obsessions/compulsions (<math>P &lt; 0.01</math>).</p>
<p>Mazidi et al. (2016)<sup>46</sup></p>	<p><b>Study design:</b></p> <p>Randomized, double blind, placebo controlled</p> <p><b>Country:</b> Iran</p> <p><b>Sample size:</b> 60 enrolled, 54 completed</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><b>Age in years (average):</b> 43</p>	<p>100 mg Saffron (stigma) OR Placebo</p>	<p><b>Outcomes measured:</b></p> <p>Depression measured using BDI</p> <p>Anxiety measured using BAI</p>	<p>The BDI and BAI scores significantly decreased in the Saffron group compared to Placebo from baseline to endpoint (<math>P &lt; 0.001</math>).</p>

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

Modabbernia et al. (2012) <sup>48</sup>	<p><b>Study design:</b> Randomized, double blind, placebo controlled</p> <p><b>Country:</b> Iran</p> <p><b>Sample size:</b> 36 enrolled, 30 completed</p> <p><b>Total study period:</b> 4 weeks</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 weeks prior to entry).</p> <p><b>Age in years (average):</b> 38</p>	<p>30 mg Saffron (stigma) AND 40 mg Fluoxetine OR Placebo AND 40 mg Fluoxetine</p>	<p><b>Outcomes measured:</b> Depression measured using HDRS</p> <p><b>Outcomes measured at:</b> Baseline and week4 (endpoint)</p>	<p>No significant difference from baseline to endpoint for HDRS scores between Saffron (coupled with Fluoxetine) and Placebo (coupled with Fluoxetine) groups (<math>P = 0.178</math>).</p>
Moshiri et al. (2006) <sup>49</sup>	<p><b>Study design:</b> Randomized, double blind, placebo controlled</p> <p><b>Country:</b> Iran</p> <p><b>Sample size:</b> 40 enrolled, 36 completed</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 weeks prior to entry.</p>	<p>30 mg Saffron (petal) OR Placebo</p>	<p><b>Outcomes measured:</b> Depression measured using HAM-D-17</p> <p><b>Outcomes measured at:</b> Baseline, week 1, week 2, week 4 and week 6 (endpoint)</p>	<p>The HAM-D-17 score significantly decreased in both the Saffron and Placebo groups from baseline to endpoint (<math>P &lt; 0.001</math>). However, the Saffron group had significantly lower HAM-D-17 scores at endpoint</p>

	<b>Total study period:</b> 6 weeks	<b>Age in years (average):</b> 35			compared to Placebo ( $P < 0.001$ )
Noorbala et al. (2005) <sup>24</sup>	<b>Study design:</b> Randomized, double blind, parallel group  <b>Country:</b> Iran  <b>Sample size:</b> 40 enrolled, 38 completed  <b>Total study period:</b> 6 weeks	Male and female outpatients who met DSM-IV criteria for mild-to-moderate depression based on the SCID-IV  <b>Age in years (average):</b> 36	30 mg Saffron (stigma) OR 20 mg Fluoxetine	<b>Outcomes measured:</b> Depression measured using HAM-D-17  <b>Outcomes measured at:</b> 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) <sup>31</sup>	<b>Study design:</b> Randomized, double blind, placebo controlled  <b>Country:</b> 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	<b>Outcomes measured:</b> Depression measured using BDI	The BDI score significantly decreased in both the Saffron (coupled with Fluoxetine) and Placebo (coupled with Fluoxetine)

	<p><b>Sample size:</b> 40 enrolled, 30 completed</p> <p><b>Total study period:</b> 4 weeks</p>	<p><b>Age in years (average):</b> 43</p>		<p><b>Outcomes measured at:</b> Baseline and week 4 (endpoint)</p>	<p>groups from baseline to endpoint (<math>P &lt; 0.003</math> and <math>P &lt; 0.000</math>, respectively). No significant difference at endpoint between the two groups (<math>P = 0.560</math>).</p>
Shahmansouri et al. (2013) <sup>25</sup>	<p><b>Study design:</b> Randomized, double blind, parallel group</p> <p><b>Country:</b> Iran</p> <p><b>Sample size:</b> 44 enrolled, 40 completed</p> <p><b>Total study period:</b> 6 weeks</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.</p> <p>Participants had also undergone Percutaneous Coronary Intervention (PCI) in the last 6 months</p> <p><b>Age in years (average):</b> 53</p>	<p>30 mg Saffron (stigma) OR 40 mg Fluoxetine</p>	<p><b>Outcomes measured:</b> Depression measured using HDRS</p> <p><b>Outcomes measured at:</b> Baseline, week 3 and week 6 (endpoint)</p>	<p>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 (<math>P = 0.70</math>).</p>

Tabeshpour et al. (2017) <sup>30</sup>	<p><b>Study design:</b> Randomized, double blind, placebo controlled</p> <p><b>Country:</b> Iran</p> <p><b>Sample size:</b> 78 enrolled, 60 completed</p> <p><b>Total study period:</b> 8 weeks</p>	<p>Breastfeeding mothers with mild-to-moderated depression based on “clinical interviews”</p> <p><b>Age in years (average):</b> 36</p>	<p>30 mg Saffron (stigma) OR Placebo</p>	<p><b>Outcomes measured:</b> Depression measured using BDI-II</p> <p><b>Outcomes measured at:</b> Baseline, week 4 and week 8 (endpoint)</p>	<p>The BDI score significantly decreased in both the Saffron and Placebo groups from baseline to endpoint (<math>P &lt; 0.003</math> and <math>P &lt; 0.01</math>, respectively). However, the Saffron group had significantly lower BDI scores at endpoint compared to Placebo (<math>P &lt; 0.001</math>).</p>
Talaee et al. (2015) <sup>32</sup>	<p><b>Study design:</b> Randomized, double blind, placebo controlled</p> <p><b>Country:</b> Iran</p> <p><b>Sample size:</b> 46 enrolled, 40 completed</p>	<p>Male and female outpatients who met DSM-IV criteria for major depression based on the SCID-IV</p> <p><b>Age in years (average):</b> 36</p>	<p>30 mg Saffron(crocin) AND 20mg Fluoxetine; OR 50mg Sertraline; OR 20mg Citalopram -OR-</p>	<p><b>Outcomes measured:</b> Depression measured using BDI Anxiety measured using BAI</p>	<p>The BDI and BAI scores significantly decreased in both groups from baseline to endpoint (<math>P &lt; 0.0001</math>). However, the Saffron group had significantly lower BDI and BAI scores at endpoint</p>



	<b>Total study period:</b> 4 weeks		Placebo AND 20mg Fluoxetine; OR 50mg Sertraline; OR 20mg Citalopram	Bipolar Disorder measured using MDQ, Mood Disorder Questionnaire <b>Outcomes measured at:</b> Baseline and week 4 (endpoint)	compared to Placebo ( $P < 0.0001$ ).  *Data for MDQ not reported
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\*Only outcomes of interest (e.g. depression and anxiety symptoms) were extracted and are presented.