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The effects of saffron (*Crocus sativus L.*) on mental health parameters and C-reactive protein: A meta-analysis of randomized clinical trials

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ABSTRACT

Background: The findings of trials investigating the effects of saffron (*Crocus sativus* L.) supplementation on depression, anxiety, and C-reactive protein (CRP) are inconsistent. The current meta-analysis of randomized controlled trials (RCTs) was carried out to assess the effects of saffron (*Crocus sativus* L.) administration on mental health parameters and CRP levels.

Methods: Two independent authors systematically searched online databases including EMBASE, Scopus, PubMed, Cochrane Library, and Web of Science from inception until 30th July 2019. Cochrane Collaboration risk of bias tool was applied to assess the methodological quality of included trials. The heterogeneity among the included studies was assessed using Cochrane's Q test and I-square (I^2) statistic. Data were pooled using a random-effects model and weighted mean difference (WMD) was considered as the overall effect size.

Results: Twenty one trials were included in this meta-analysis. Consumption of saffron resulted in a significant reduction in Beck Depression Inventory (BDI) (11 studies with 12 effect size) (WMD: −4.86; 95 % CI: −6.58, −3.14), Beck Anxiety Inventory (BAI) (5 studies) (WMD: −5.29; 95 % CI: −8.27, −2.31) and Pittsburgh Sleep Quality Index (PSQI) scores (3 studies with 4 effect size) (WMD: −2.22; 95 % CI: −2.73, −1.72). Saffron intake did not affect Hamilton Depression Rating Scale (HDRS-D), Hamilton Anxiety Rating Scale (HARS-A) scores and C-reactive protein (CRP) levels.

Conclusions: This meta-analysis demonstrated that saffron intake significantly reduced BDI, BAI and PSQI scores, but did not affect HDRS-D, HARS-A scores and CRP levels.

1. Introduction

Depression is one of the most prevalently diagnosed psychiatric disorders. Almost, 1 in 5 adults in the US population report experiencing at least one period of major depression in their life, with women having twice as big chance to develop depression and anxiety.[1] Symptoms of depression include psychological parameters, physical signs and behavioral symptoms, including depressed mood, loss of interest to any action, pessimism, fatigue, feelings of worthlessness, reduced ably to think or concentrate, tearfulness, thoughts of suicide or death and weight loss, sleep and appetite disorders and anhedonia.[2,3] Patients with depression may suffer also from anxiety,[4] another common mental health disorder which is associated with poor quality of life.[5]

Recently, cognitive behavior therapy (CBT) for mild to moderate depression represents an attractive option for major depressive disorder and insomnia.[6] In a meta-analysis conducted by Okumura and Ichikura,[7] CBT had better performance compared to non-active treatments. But this treatment is generally scarce by noncompliance and few trained therapists. Therefore, *Crocus sativus* L. might be considered as

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an alternative therapy for mental disorder and metabolic syndrome. *Crocus sativus L.*, commonly known as saffron, belongs to the Iridaceae family.[8] The effects of saffron occur due to three main secondary metabolites, including crocin, picrocrocin and safranal.[9,10] Current evidence suggests the beneficial effects of saffron on parameters of mental health and treatment of central nervous system disorders in patients with depression and without depression. However, randomized clinical trials (RCTs) of the effects of saffron for treatment of depression and anxiety have not been systematically evaluated and the results are controversial. In a study by Ghajar et al.,[11] 30 mg/day of saffron administration for 6 weeks to patients with major depressive disorder (MDD) and anxious distress significantly improved depression and anxiety scores. Taking 30 mg/day of crocin for 12 weeks by patients with metabolic syndrome (MetS) reduced Beck Depression Inventory (BDI) score.[12] In another study, taking 30 mg/day *Crocus sativus* L. for 6 weeks had a significant impact on Hamilton depression rating scale (HDRS), i.e. it showed antidepressive effects.[13] However, fluoxetine combined with saffron (30 mg/day) for 4 weeks did not affect BDI score when compared with fluoxetine as mono-therapy and placebo in patients with MDD.[14]

Although it has been proposed that saffron may improve parameters of mental health, including depression and anxiety, the results of some studies did not confirm this.[15] Therefore, this meta-analysis was performed to summarize all the existing RCTs evidence and to evaluate the effects of saffron intake on parameters of mental health and CRP.

2. Materials and methods

The present study to the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) statement guideline for performing and reporting.[16]

2.1. Search and studies selection strategies

Scientific international databases, including PubMed, Scopus, ISI (Web of Science), Cochrane Central Register of Controlled Trials, EMBASE, Google Scholar, contact with the authors and scanning the reference list of included studies were searched for relevant studies published from incent until 30th July 2019. A search strategy was developed using the following MeSH and text keywords; intervention, (Crocus[MeSH] OR Crocus[tiab] OR colchicum[MeSH] OR colchicum [tiab] OR "*Crocus sativus*"[MeSH] OR "*Crocus sativus*"[tiab] OR crocin [tiab] OR crocetin[tiab] OR Saffron*[tiab] OR safranal[MeSH] OR safranal [tiab]) AND (depression[MeSH] OR depression[tiab] OR "depressive symptoms"[tiab] OR anxiety[MeSH] OR anxiety[tiab] OR "beck depression inventory"[tiab] OR BDI[tiab] OR BDI-II[tiab] OR "beck anxiety inventory"[tiab] OR BAI[tiab] OR "Hamilton Rating Scale"[tiab] OR Hamilton[tiab] OR "Hamilton rating scale for depression"[tiab] OR HDRS[tiab] OR "Hamilton depression rating scale"[tiab] OR HAMD[tiab] OR "HDRS-D"[tiab] OR "Hamilton rating scale for anxiety"[tiab] OR "HDRS-A"[tiab] OR "Pittsburgh sleep quality index"[tiab] OR PSQI[tiab] OR inflammation[MeSH] OR inflammation [tiab] OR "inflammatory markers"[tiab] OR "C-reactive protein"[MeSH] OR "C-reactive protein"[tiab] OR CRP[tiab])

2.2. Inclusion and exclusion criteria

RCTs complying with the following criteria were included in meta-analysis: human trials with either cross-over design or parallel, trials with data on the effects of saffron on parameters of mental health and CRP with standard deviation (SD) and related 95 % confidence interval (CI) for the both intervention and placebo groups). Other studies such as animal experiments, *in vitro* studies, case reports, observational studies, trials without a control group, and studies that did not achieve the least quality score were excluded from this meta-analysis.

2.3. Data extraction and quality assessment

Two independent authors (AG and EA) screened the articles based on the eligibility criteria. As the first step the titles and abstracts of studies were reviewed. Then, the full-text of relevant studies was assessed to ascertain the suitability of a study for the meta-analysis. Any disagreement was resolved by the judgment of the third author (ZA).

Following data were taken from selected studies: the first authors' name, study location, year of publication, sample size, age, study design, dosage of saffron, duration of study, type of the disease, the mean and SD for BDI, BAI, HAMD and CRP in the intervention and control groups. The quality of the selected RCTs was independently assessed by the same authors using the Cochrane Collaboration risk of bias tool[17] based on the following criteria: "randomization generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, and selective outcome reporting, and other sources of bias".

2.4. Data synthesis and statistical analysis

The effects of saffron consumption on the changes of the following parameters were calculated: 1) BDI, 2) BAI, 3) HAMD and 4) CRP. Weighted mean difference (WMD) with 95 % CI was used for pooling data to determine the effect sizes. The change score approach was used to calculate the effect size of saffron intake on the analyzed parameter. The random-effect model was used to report the pooled effect sizes using 95 % CI.[18] To calculate the SD changes, the following formula was used: SD = square root [(SD pre-treatment)^2 (SD posttreatment)2 - (2R × SD pre-treatment × SD post-treatment)], correlation coefficient (R-value) was considered 0.9.[19] When an SEM or SE was reported instead of SD, the SD was calculated based on the following formula: SD = SEM × √n (n = sample size in each group).

2.5. Heterogeneity and publication bias

Heterogeneity of included studies was assessed using Cochrane's Q test (with significant P-value < 0.1) and I-square test (I^2 greater than 50 percent showing significant heterogeneity). The funnel plot, as well as the Beggs's and Egger's regression tests were used to determine the publication bias. STATA 11.0 (Stata Corp., College Station, TX) was applied for data analysis.

3. Results

3.1. Characteristics of studies

Twenty one trials which were published between 2005 and 2019 were included in this systematic review and meta-analysis. Flow-diagram for study selection is shown in Fig. 1. 1052 subjects, 563 in intervention and 489 in control groups, were enrolled in included studies. Characteristics of included studies are summarized in Table 1. The dosages of saffron varied between 22 to 1000 mg/day, with a duration range between 4 and 12 weeks. Results of quality assessment showed that the quality of all included studies was high.

3.2. The effects of saffron on parameters of mental health

Consumption of saffron resulted in a significant reduction in BDI (11 studies with 12 effect size) (WMD: -4.86; 95 % CI: -6.58, -3.14) (Table 2 & Fig. 2A), BAI (5 studies) (WMD: -5.29; 95 % CI: -8.27, -2.31) (Table 2 & Fig. 2C) and PSQI scores (3 studies with 4 effect size) (WMD: -2.22; 95 % CI: -2.73, -1.72) (Table 2 & Fig. 2D). Saffron intake did not affect HDRS-D (6 studies) (WMD: -1.61; 95 % CI: -5.81, 2.58) (Table 2 & Fig. 2B) and HARS-A scores (WMD: -2.74; 95 % CI: -5.76, 0.27) (Table 2 & Fig. 2E). The findings of the effects of saffron on BDI and BAI did not change in subgroup analysis (Table 3). However, HDRS-D score became

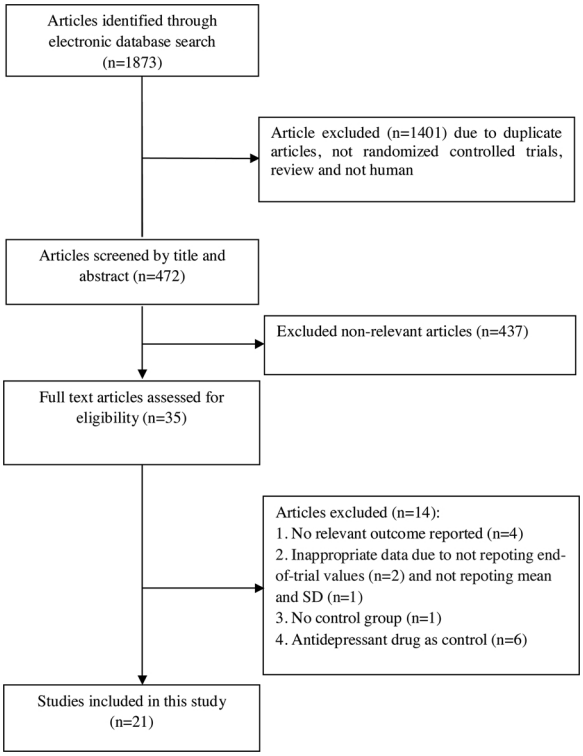

Fig. 1. Literature search and review flowchart for selection of studies.

significant in studies using saffron in non-depressed (WMD: 3.76; 95 % CI: 2.93, 4.58), in studies in which the duration of intervention was ≥8 (WMD: 3.32; 95 % CI: 2.52, 4.11), in subjects with age < 50 years (WMD: 3.86; 95 % CI: 2.94, 4.79) and > 50 years (WMD: 0.94; 95 % CI: 0.01, 1.86) (Table 3).

3.3. The effects of saffron on CRP levels

Saffron intake did not affect CRP levels (WMD: -0.71; 95 % CI: -1.66, 0.23) (Table 2 & Fig.2F).

3.4. Publication bias

Publication bias was evaluated by Egger's test. The results indicated no evidence of publication bias in the meta-analysis for the effects of saffron intake on HARS-A (P = 0.660), BAI (P = 0.857) and CRP (P = 0.825). However, there was publication bias for HDRS-D (P = 0.013), BDI (P < 0.001) and PSQI (P = 0.015).

4. Discussion

Depression and anxiety are serious mental disorders.[20,21] Various drugs have been used to treat these mental disturbances, but they are associated with significant adverse effects. Some studies have investigated the beneficial effects of herbal medicines, including saffron in the treatment of depression and anxiety.[22–24] The purpose of our study was to present a meta-analysis of RCTs examining the effectiveness of *Crocus sativus* L., commonly known as saffron, on parameters of mental health and CRP. This meta-analysis demonstrated that saffron intake significantly reduced BDI, BAI and PSQI scores, but did not affect HDRS-D, HARS-A scores and CRP levels. Few meta-analyses have previously evaluated the effects of consuming saffron on symptoms of depression and anxiety. However, the results of one of these meta-analysis are questionable because of evidence of publication bias and lack of regional diversity and the other meta-analysis was more directed towards the effects of saffron on the severity of depression and comparison with tested antidepressant drugs.[25,26] The results of another meta-analysis indicated that the effects of saffron on MDD did not differ from the effects of synthetic antidepressants.[27] However, previous meta-analyses have assessed the effects saffron intake on symptoms of depression and anxiety,[25] and only depression,[27,28] we have evaluated the effects of saffron on mental health parameters such as BDI, BAI, PSQI, HDRS-D and HARS-A scores, and CRP levels.

4.1. Effects on parameters of mental health

This meta-analysis showed that saffron intake significantly reduced BDI, BAI and PSQI scores, but did not affect HDRS-D and HARS-A scores. Several interesting data have been reported about the antidepressant and anti-anxiety properties of saffron based upon preclinical and clinical studies. A number of RCTs demonstrated that saffron and its active constituents have antidepressant properties similar to those of antidepressant drugs such as fluoxetine, imipramine and citalopram, but with less adverse effects. An older meta-analysis by Hausenblas et al. [28], indicated that saffron might improve symptoms of depression in adults with MDD but this meta-analysis has included only trials from one country. Data from two reviews have suggested that saffron can improve the symptoms and effects of depression, premenstrual syndrome, sexual dysfunction and infertility, and excessive snacking behaviors.[28,29] In the study by Mazidi et al.,[30] taking 50 mg/twice daily saffron for 12 weeks by patients with anxiety and depression resulted in a significant reduction in BDI and BAI scores. In another study, crocin administration for 4 weeks in patients with MDD had favorable effects on mental health parameters, including depression, anxiety, general health, and mood disorders.[31] Saffron intake at a dosage of 15 mg/twice daily for 8 weeks by mothers with mild-to-moderate postpartum depressive disorder significantly reduced their BDI-II scores.[32] However, in a pilot trial comparing the efficacy of *Crocus sativus* L. with fluoxetine in depressed adult outpatients by Akhondzadeh Basti et al.[33], petal of C. sativus consumption at a dosage of 15 mg/day for 8 weeks was found to be effective similar to fluoxetine in the treatment of mild to moderate depression and there were no significant differences in the two groups concerning adverse effects.. In another study, comparing the efficacy of 30 mg/day saffron with 40 mg/day fluoxetine for 6 weeks, saffron capsules intake showed the same antidepressant efficacy when compared with fluoxetine in patients with mild to moderate depression who had undergone percutaneous coronary intervention.[13] The effects of saffron on parameters of mental health might be a result of a synergistic function of several constituents, including crocin, safranal, picrocrocin, and flavonoids.[34] The exact mechanism of action of saffron in the brain and its effects on mental health scores is still not clear. Saffron might inhibit reuptake of monoamine neurotransmitters, including norepinephrine, dopamine, and serotonin in synapses.[35] The effects saffron on mental health parameters may be also due to its antioxidant effects and inhibiting pro-inflammatory profiles and free radicals.[36]

4.2. Effects on CRP levels

We found that saffron administration did not affect CRP levels. Results of saffron administration on inflammatory markers are controversial. In a study by Hosseini et al.[37], saffron administration at a dosage of 100 mg/day for 8 weeks in subjects with allergic asthma decreased significantly hs-CRP levels. We have previously shown that taking crocin for 8 weeks by subjects under methadone maintenance treatment, was associated with a significant reduction in hs-CRP levels.[38] However, taking saffron (1 g/day) for 8 weeks in patients with type 2 diabetes mellitus (T2DM) did not have any effects on CRP levels.[39] Different study designs, lack of considering baseline values of dependent variables and different characteristics of study patients, different dosages of saffron as well as different duration of studies might be some of the reasons for these discrepant findings. Anyhow, intake of saffron and crocin may decrease inflammatory markers

Table 1
Characteristics of primary clinical trials included in the meta-analysis.

Authors (Ref)	Publication year	Sample size (control/ intervention)	Country/population	Intervention (name and daily dose)	Duration	Age (y) (control, intervention)	Presented data	Type of control
Akhondzadeh et al [20]	2005	16/19	Iran/mild to moderate depression	30 mg/day saffron	6 weeks	35.25 ± 6.12, 37.30 ± 8.56	HDRS-D	Placebo
Moshiri et al [42]	2006	17/19	Iran/mild to moderate depression	30 mg/day saffron (petal)	6 weeks	35.85 ± 5.63, 35.45 ± 8.19	HDRS-D	Placebo
Agha-Hosseini et al [43]	2008	23/24	Iran/premenstrual syndrome (women)	30 mg/day saffron	8 weeks	33.45 ± 7.61, 35.10 ± 7.79	HDRS-D	placebo
Azimi et al [39]	2014	39/42	Iran/type 2 diabetes mellitus	1 g/d saffron in combination with three glasses of black tea	8 weeks	53.64 ± 8.11, 57.02 ± 6.48	CRP	Three glasses of black tea
Talaei et al [31]	2015	20/20	Iran/major depressive disorder	30 mg/day crocin + SSRI drug	4 weeks	36.5 ± 7.67, 35.9 ± 7.10	BDI, BAI	Placebo + SSRI drug
Mazidi et al [30]	2016	30/24	Iran/patients with anxiety and depression	100 mg/day saffron	12 weeks	43.6 ± 8.83, 42.8 ± 10.65	BDI, BAI	Placebo
Sahraian et al [14]	2016	11/19	Iran/major depression	30 mg/day saffron +20 mg/day fluoxetine	4 weeks	43.3 ± 4.2, 41.2 ± 5.1	BDI	Placbo +20 mg/day fluoxetine
Milajerdi et al [44]	2016	25/25	Iran/type 2 diabetes mellitus with mild to moderate anxiety and depression	30 mg/day saffron hydro-alcoholic extract	8 weeks	55.42 ± 7.58, 54.57 ± 6.96	BDI, BAI	Placebo
Tabeshpour et al [32]	2017	30/30	Iran/mothers suffering from mild-to-moderate postpartum depression	30 mg/day saffron	8 weeks	28 ± 40.4, 28.1 ± 28.9	BDI	Placebo
Jam et al [12]	2017	17/16	Iran/depression in metabolic syndrome	30 mg/day crocin	8 weeks	48.37 ± 5.43, 45.34 ± 6.41	BDI	Placebo
Kell (a) et al [45]	2017	16/37	Australia/self-reporting low mood but not diagnosed with depression (healthy adults)	22 mg/day saffron	4 weeks	40.38 ± 13.97, 36.7 ± 14.59	PSQI	Placebo
Kell (b) et al [45]	2017	17/39	Australia/self-reporting low mood but not diagnosed with depression (healthy adults)	28 mg/day saffron	4 weeks	40.38 ± 13.97, 40.4 ± 12.71	PSQI	Placebo
Jafarnia et al [46]	2017	20/20	Iran/generalized anxiety disorder	450 mg/day saffron +50 mg sertraline	4 weeks	32.40 ± 6.74, 29.65 ± 8.45	HARS-A	Placebo +50 mg sertraline
Abedimanesh (b) et al [47]	2017	10/20	Iran/coronary artery disease	30 mg/day saffron aqueous extract	8 weeks	56.63 ± 6.08, 53.70 ± 6.23	BDI	Placebo
Abedimanesh (a) et al [47]	2017	9/19	Iran/coronary artery disease	30 mg/day crocin	8 weeks	56.63 ± 6.08, 56.16 ± 7.22	BDI	Placebo
Kermani et al [48]	2017	22/22	Iran/metabolic syndrome	100 mg/day saffron	12 weeks	42.59 ± 8.44, 43.64 ± 11.17	CRP	Placebo
Moazen-Zadeh et al [15]	2018	14/15	Iran/patients undergoing coronary artery bypass grafting	30 mg/day saffron	12 weeks	56.61 ± 5.6, 58.14 ± 4.43	HARS-A HDRS-D	Placebo
Kashani et al [49]	2018	28/28	Iran/women with post-menopausal hot flashes and depression	30 mg/day saffron	6 weeks	55.43 ± 5.46, 55.71 ± 6.57	HDRS-D	Placebo
Jelodar et al [50]	2018	20/20	Iran/major depression	30 mg/day saffron +20 mg/day fluoxetine	4 weeks	20-55	BDI	Placbo +20 mg/day fluoxetine
Jalali et al [51]	2018	28/29	Iran/recovered methamphetamine consumers with HIV/AIDS	30 ml/day saffron	8 weeks	32.91 ± 4.19, 33.12 ± 3.71	BDI	Placebo
Milajerdi et al [52]	2018	25/25	Iran/type 2 diabetes mellitus with mild to moderate anxiety and depression	30 mg/day saffron hydro-alcoholic extract	8 weeks	55.42 ± 7.58, 54.57 ± 6.96	PSQI, HDRS-D, HARS-A	Placebo
Khalatbari-Mohseni et al [53]	2019	25/25	Iran/patients under methadone maintenance treatment	30 mg/day crocin	8 weeks	41.4 ± 8.8, 40.1 ± 9.3	BDI, BAI, PSQI	Placebo
Ghaderi et al [38]	2019	27/26	Iran/patients under methadone maintenance treatment	30 mg/day crocin	8 weeks	45.6 ± 9.9, 44.5 ± 9.4	BDI, BAI, CRP	Placebo

Table 2
The effects of saffron intake on parameters of mental health and C-reactive protein.

Variables	Number of effect sizes	Weighted mean difference	CI 95 %	P- value	Heterogeneity	
					I^2 (%)	P- value heterogeneity
BDI	12	−4.86	−6.58, -3.14	< 0.001	93.0 %	< 0.001
HDRS-D	6	−1.61	−5.81, 2.58	0.452	97.1 %	< 0.001
BAI	5	−5.29	−8.27, -2.31	< 0.001	93.9 %	< 0.001
PSQI	4	−2.22	−2.73, -1.72	< 0.001	3.6 %	0.375
HARS-A	3	−2.74	−5.76, 0.27	0.074	90.9 %	< 0.001
CRP	3	−0.71	−1.66, 0.23	0.139	89.4 %	< 0.001

BDI, Beck Depression Inventory; HDRS-D, Hamilton Depression Rating Scale; BAI, Beck Anxiety Inventory; PSQI, Pittsburgh Sleep Quality Index; HARS-A, Hamilton Anxiety Rating Scale; CRP, C-reactive protein.

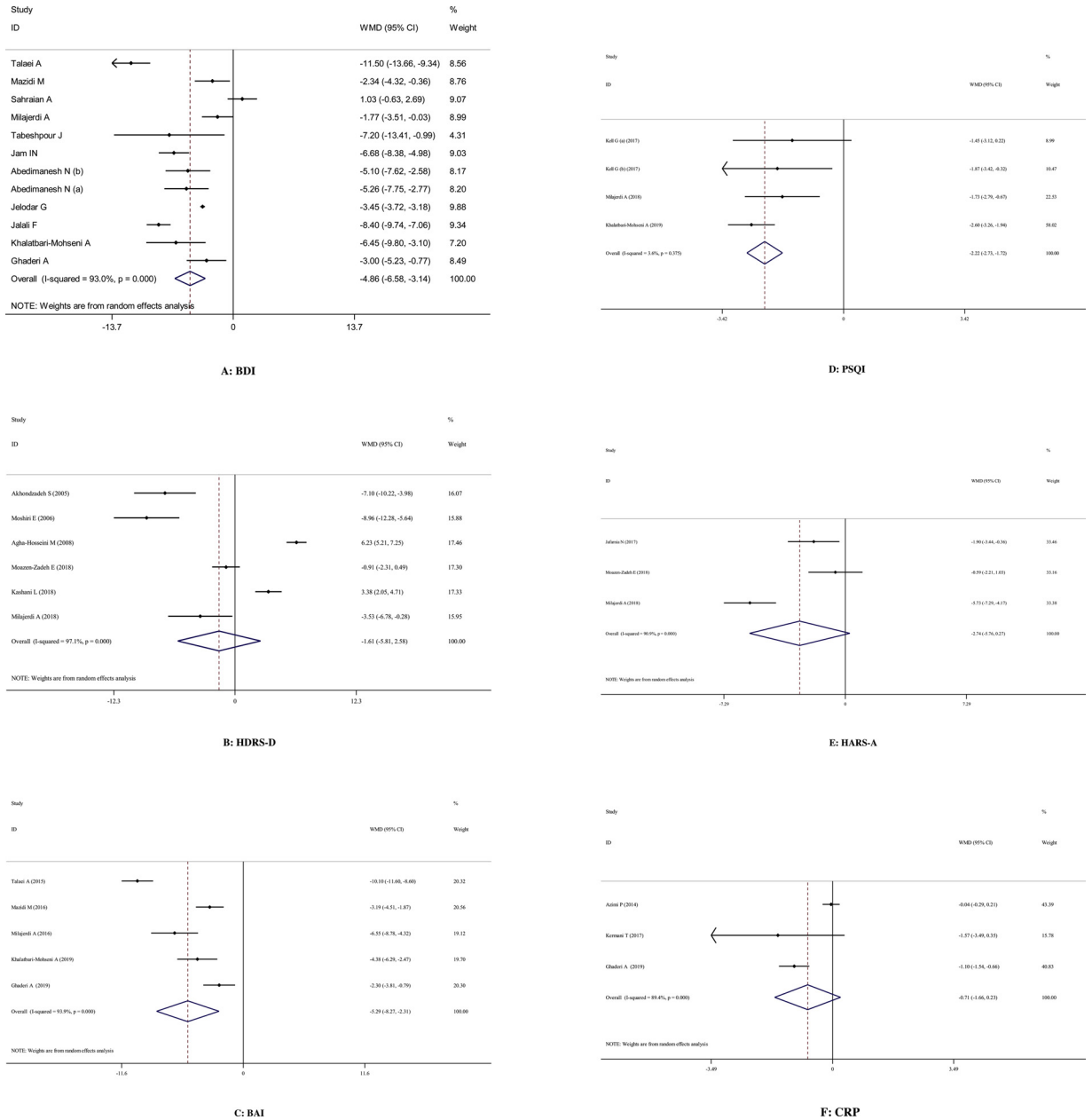

Fig. 2. A–F. Meta-analysis parameters of mental health and CRP weighted mean difference estimates for A) BDI, B) HDRS-D, C) BAI, D) PSQI, E) HARS-A, and F) CRP levels in the saffron and placebo groups (CI = 95 %).

Table 3
Subgroup analyses of saffron intake on parameters of mental health.

	NO	WMD (95 %CI)	P within group	P heterogeneity	I^2 (%)	Between-study I^2 (%)
Subgroup analyses of saffron supplementation on BDI						
Trial duration (week)						
< 8	3	−3.45 (-3.72, -3.19)	< 0.001	< 0.001	97.5 %	< 0.001
≥8	9	−5.26 (-5.95, -4.57)	< 0.001	< 0.001	84.7 %	
dosage						
≤30	11	−3.71 (-3.96, -3.46)	< 0.001	< 0.001	93.6 %	0.176
> 30	1	−2.34 (-4.31, -0.36)	0.020	–	–	
Patients						
Depression	7	−3.48 (-3.73, -3.22)	< 0.001	< 0.001	94.1 %	< 0.001
Non- depressed	5	−6.43 (-7.35, -5.50)	< 0.001	0.001	79.3 %	
Age						
< 50	9	−3.70 (-3.95, -3.44)	< 0.001	< 0.001	94.7 %	0.697
> 50	4	−3.45 (-4.69, -2.20)	< 0.001	0.027	72.4 %	
Subgroup analyses of saffron supplementation on HDRS-D						
Trial duration (week)						
< 8	3	0.47 (-0.67, 1.62)	0.419	< 0.001	97.2 %	< 0.001
≥8	3	3.32 (2.52, 4.11)	< 0.001	< 0.001	97.6 %	
Patients						
Depression	4	0.02 (-1.05, 1.11)	0.959	< 0.001	96.1 %	< 0.001
Non- depressed	2	3.76 (2.93, 4.58)	< 0.001	< 0.001	98.5 %	
Age						
< 50	3	3.86 (2.94, 4.79)	< 0.001	< 0.001	98.4 %	< 0.001
> 50	3	0.94 (0.01, 1.86)	0.046	< 0.001	92.6 %	
Subgroup analyses of saffron supplementation on BAI						
Trial duration (week)						
< 8	1	−10.10 (-11.60, -8.59)	< 0.001	–	–	< 0.001
≥8	4	−3.60 (-4.42, -2.78)	< 0.001	0.014	71.6 %	
dosage						
≤30	4	−5.89 (-6.75, -5.03)	< 0.001	< 0.001	94.5 %	0.001
> 30	1	−3.19 (-4.50, -1.87)	< 0.001	–	–	
Patients						
Depression	3	−6.25 (-7.16, -5.34)	< 0.001	< 0.001	95.6 %	< 0.001
Non- depressed	2	−3.10 (-4.28, -1.91)	< 0.001	0.094	64.4 %	
Age						
< 50	4	−4.92 (-5.68, -4.16)	< 0.001	< 0.001	95.3 %	0.177
> 50	1	−6.55 (-8.78, -4.31)	< 0.001	–	–	

BDI, Beck Depression Inventory; HDRS-D, Hamilton Depression Rating Scale; BAI, Beck Anxiety Inventory; WMD, weighted mean differences; CI, confidence interval.

through downregulation of mitogen-activated protein kinase (MAPK) and MAPKAP signaling pathway and miRNA-122 expression[40] and inhibiting apoptosis.[41]

This meta-analysis has several limitations. Various doses of saffron and different types of saffron as powder, extracts and pure crocin were administered in the included studies that may have different effects on mental health parameters. Due to the heterogeneity between studies, as a result of variations in the dosage, frequency, or duration of saffron intake, the results of this meta-analysis should be interpreted with caution. We were unable to evaluate the dose response association between supplementation dose and mental health parameters due to the relatively small number of studies included. Also, we did not evaluate the residual confounding and bias of each study that could not be addressed through pooling. Heterogeneity for CRP and HARS-A was high. This may be due to a low quality of methodology within the papers. Therefore, this should be considered in the interpretation of our findings.

However, there are also several strengths of this study. More studies which were included in this meta-analysis and longer period of supplementation in included trials have provided added value to this meta-analysis. In addition, we relied on independent judgment in which different reviewers independently performed the systematic review process.

5. Conclusions

This meta-analysis demonstrated that saffron intake significantly reduced BDI, BAI and PSQI scores, but did not affect HDRS-D, HARS-A scores and CRP levels.

Author contributions

AG and ZA contributed in conception, design, statistical analysis and drafting of the manuscript. OA, ZR, EA, FK and HM, contributed in conception, data collection and manuscript drafting. The final version was confirmed by all authors for submission.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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