

The effects of crocin on the symptoms of depression in subjects with metabolic syndrome

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Abstract

Background. Studies have suggested that metabolic syndrome (MetS) is associated with increased depressive symptoms, and reducing depression in subjects with MetS is important. Crocin, an active component of saffron, has useful properties for subjects with MetS, including antidepressant properties.

Objectives. The aim of the study was to assess the effect of a preparation of crocin on the symptoms of depression in subjects with MetS, and the relationship between changes in those symptoms and the serum pro-oxidant/anti-oxidant balance (PAB).

Material and methods. This sub-study was carried out on 34 subjects with MetS from the authors' previous randomized double-blind controlled clinical trial (RCT), all of whom met the inclusion criteria for this study. The subjects were randomly assigned to treatment and placebo groups ($n = 17$ in each group) and received each 30 mg of crocin (2 tablets of 15 mg) or placebo for 8 weeks. Depressive symptoms were assessed using the Beck Depression Inventory (BDI). The BDI questionnaire was completed for each subject at the baseline and at the end of the 8th week of treatment. Blood samples were taken from the subjects before and after the intervention period. Statistical analyses were performed using the SPSS for Windows, v. 16 (SPSS Inc., Chicago, USA).

Results. Out of the 34 participants enrolled, 33 completed the trial. The degree of depression decreased significantly in the crocin group ($p = 0.005$), but not in the placebo group ($p > 0.05$), and the difference between the 2 groups was statistically significant ($p = 0.013$). No significant relationship was observed between changes in depression symptoms and changes in the serum PAB ($p > 0.05$).

Conclusions. This study demonstrates that at a dose of 30 mg per day for 8 weeks, crocin reduced the symptoms of depression in subjects with MetS compared to the control group, and this effect was independent of its effect on the serum PAB.

Key words: crocin, metabolic syndrome, depression, saffron

Metabolic syndrome (MetS) is a common disorder that increases the risk of cardiovascular disease and type 2 diabetes. MetS is defined by a set of cardiovascular risk factors including abdominal obesity, hypertension, hyperglycemia and dyslipidemia (high blood triglycerides, low high-density lipoprotein).¹ MetS has high prevalence worldwide, and also in Iran.² Some studies show that MetS is associated with an increased risk of depressive symptoms.^{3,4} Epidemiological studies show that the chances of patients with MetS developing depression are high and that there is a positive association between components of the metabolic syndrome, including abdominal obesity, hypertriglyceridemia and low HDL cholesterol, and depression.^{5,6} Previous studies have pointed to the importance of early detection and management of depression in patients with MetS.⁷

There is evidence suggesting that a significant multifaceted and possibly reciprocal relationship exists between depression and MetS.⁷⁻⁹ First, increased inflammatory cytokines and leptin resistance occur in patients with MetS, which increases their chances of developing depression.^{5,7} Evidence also suggests that some metabolic abnormalities in MetS, such as impaired glucose homeostasis and mitochondrial respiration can contribute to the pathophysiology of depression.¹⁰ It has also been suggested that possible subclinical vascular damage in Mets can contribute to the development of depressive symptoms.¹¹ Also, certain components of MetS, including obesity, may be associated with decreased self-esteem and increase the chances of depression.¹²

At the same time, MetS may be characteristic for subjects with depression leading an unhealthy lifestyle, because their diet often contains large amounts of fats and carbohydrates but only small amounts of vegetables, fruits and whole grains. Also, they do not engage in enough physical activity, and these factors make them predisposed to metabolic syndrome.^{5,7,13} Depression is also associated with an increase in chronic inflammation and insulin resistance, and some neuroendocrine effects that can increase the risk of MetS.⁷

Oxidative stress is an imbalance between the production of pro-oxidants and anti-oxidants, with an excess of pro-oxidants. Studies have confirmed the contribution of oxidative stress in the etiology of both depression and MetS.^{14,15} Therefore, reducing oxidative stress could be one of the important goals in the treatment of both MetS and depression. The pro-oxidant/anti-oxidant balance (PAB) assay is a new and simple method to measure the balance of pro-oxidants and anti-oxidants concurrently. Evidence has shown that PAB results are comparable with approved standard assessments of oxidative stress and that they correlate with protein oxidation markers such as carbonyl, advanced glycation end products (AGEs) and advanced oxidative protein products (AOPPs).^{16,17}

Previous studies have provided evidence that saffron can be effective in improving depressive symptoms.¹⁸

Crocine is one of main active components of saffron, and animal studies have confirmed its antidepressant properties.¹⁹ In addition, previous studies have shown that crocine has anti-oxidant properties as well.¹⁹

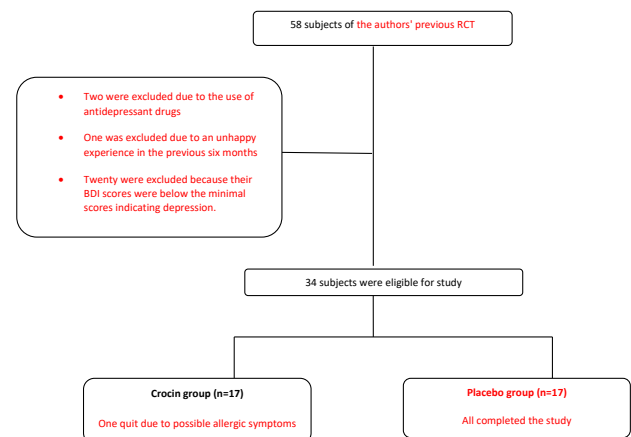
One of crocine antidepressant mechanisms may be related to its anti-oxidant property. The first objective of this study was to evaluate the effects of crocine on the symptoms of depression in subjects with metabolic syndrome. The second objective was to assess the association between changes in the symptoms of depression and the serum PAB, in order to evaluate the relationship between the anti-oxidative and antidepressant effects of crocine. As far as the authors are aware, there has been no previous research similar to this study, and there are no reports in the literature yet on the effects of crocine on depressive symptoms in humans.

Material and methods

This study is a substudy of the authors' previous randomized double-blind controlled clinical trial (RCT) on subjects with Mets, conducted at the Nutrition Clinic of Qaem Teaching Hospital, Mashhad, Iran, from April to June 2014.²⁰ The clinical trial was an approved and registered RCT, compliant with ethical standards, and written consent was obtained from all the participants. Volunteers with MetS according to the International Diabetes Federation (IDF) criteria were randomly assigned to a treatment group and a placebo group, and received either 30 mg of crocine or a placebo for 8 weeks. All subjects received similar dietary advice based on the American Heart Association (AHA) guidelines. This substudy involved 34 of the eligible RCT subjects (Fig. 1).

Exclusion criteria included pregnancy, lactation, age under 18 or over 70 years, use of antidepressant drugs, under 10 points on the Beck Depression Inventory (BDI) questionnaire, grief or unpleasant event during the previous 6 months, and a lack of compliancy in taking the pills regularly.

Fig. 1. Flow chart of the eligibility of study participants



The scores of less than 9 points on the BDI scale indicate a minimal degree of depressive symptoms. Since a drug shows its therapeutic potential in subjects that suffer from a complication rather than in non-affected subjects, this study (like the previous one) included subjects whose BDI score was 10 points or higher.²¹

Symptoms of depression

The BDI, which was used to assess depressive symptoms, includes 21 questions with 4 options for each question.²² The responses to the questions are scored from 0 to 3 according to their intensity, and the total score is used to estimate the degree of depression. The cut-off values of BDI scores to define 4 degrees of depression are 0–9 (grade 1: minimal depression), 10–18 (grade 2: mild depression), 19–29 (grade 3: moderate depression) and 30–63 (grade 4: severe depression). The BDI questionnaire was completed for each subject at the baseline and at the end of week 8 of the study.

Crocin tablets

The extraction of crocin from saffron was done according to a previously published work by the current authors, and the pill manufacturing was undertaken by the School of Pharmacy, Mashhad University of Medical Science (MUMS), Iran.²³ Each crocin tablet contained 15 mg of crocin; the placebo pills were given a similar appearance, but contained only starch and food coloring. Quality control tests were conducted under the supervision of an industrial pharmacy specialist.²⁰

Anthropometric and blood pressure assessment

Anthropometric measurements performed on all the participants included height, weight, waist circumference and hip circumference. Standing height (cm) was measured without shoes, with a wall-mounted stadiometer. Maximum hip circumference and minimum waist circumference were measured with a tape to the nearest 0.1 cm. A BC-418 bioelectrical impedance analysis device (Tanita, Tokyo, Japan) was used to measure body weight and body mass index (BMI). Blood pressure was measured on the right arm in the sitting position after at least 15 min of rest.

Blood sampling and laboratory tests

Blood samples were taken in the morning after 12 h of fasting, before and after the intervention. After centrifugation, the separated serum was stored at -80°C until the tests were run. Fasting blood lipid profile and blood glucose (FBG) were measured to diagnose metabolic syndrome; the fasting lipid profile included total cholesterol,

triglycerides, low-density lipoprotein (LDL) and high-density lipoprotein (HDL). These blood factors were measured enzymatically according to standard protocols and using the relevant commercial kits (Pars Azmoon, Tehran, Iran). The serum PAB measurement was done according to the method described in previous studies.^{16,17}

Statistical analysis

Statistical analyses were performed using the SPSS for Windows v. 16 software package (SPSS Inc., Chicago, USA). The data was analyzed using the Kolmogorov-Smirnov test to assess normality; Student's t-test or the Mann-Whitney test were used to compare baseline characteristics; the χ^2 test, Wilcoxon and Mann-Whitney tests were used to assess depression. A 2-tailed p-value < 0.05 was considered statistically significant.

Results

No significant differences were observed in the baseline characteristics of the drug group and the placebo group (Table 1). Similarly, no significant differences were observed in the baseline degree of depression between the 2 groups before the intervention (Table 1).

Out of the original 34 volunteers, 33 subjects completed the trial. One participant was excluded due to potential allergic symptoms.

The results of the analyses show that the degree of depression decreased in 68.8% of the crocin group and 29.4% of the placebo group (Fig. 2). The reduction of depression in the crocin group was statistically significant, while the reduction in the placebo group was not statistically significant. The difference in the changes in the degree of depression between the 2 groups was statistically significant at the 0.05 level (Table 2).

Fig. 2. Changes in the degree of depression in the 2 groups

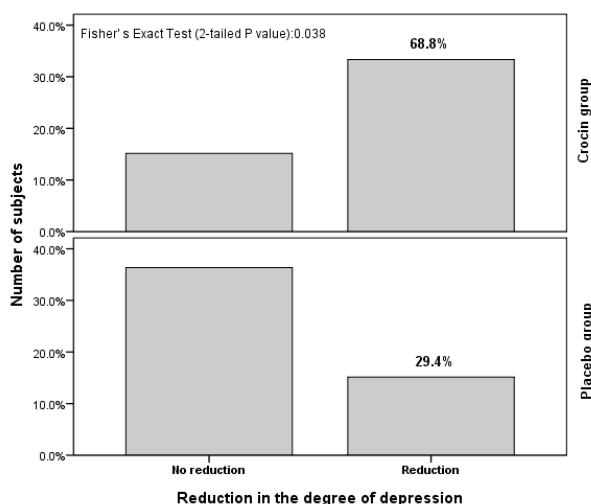


Table 1. Baseline characteristics of the study participants

Features	Case group	Control group	*p-value
Female/male (n)	12/4	10/7	p > 0.05
Age (years)	45 (34.5, 50)	48 (37, 55)	p > 0.05
Weight (kg)	83.4 (79.2, 102.2)	85.9 (79.3, 102.2)	p > 0.05
Height (cm)	159.5 (153.5, 166.2)	156 (153, 167)	p > 0.05
WC (cm)	110.7 (100.7, 120.5)	107 (102, 122.5)	p > 0.05
HC (cm)	113.0 (112.0, 121.7)	113.2(108.5, 124.5)	p > 0.05
BMI	34.25 (31.27, 36.2)	34.6 (31, 38.3)	p > 0.05
Smokers % (n)	6.2% (1)	0% (0)	p > 0.05
Diabetics** % (n)	18.7% (3)	23.5% (4)	p > 0.05
Hypertensive*** % (n)	18.7% (3)	18.7% (3)	p > 0.05
Cardiovascular disease**** % (n)	6.2% (1)	0% (0)	p > 0.05
Degree of depression*****	n (%)	n (%)	*p-value
Degree 2 (scores 10-18)	8 (50%)	10 (58%)	p > 0.05
Degree 3 (scores 19-29)	5 (31.2%)	6 (35.2%)	
Degree 4 (scores 30-63)	3 (18.7%)	1 (5.8%)	
BDI Score	18.5 (12.5, 26.5)	17 (15, 22)	

WC – waist circumference; HC – hip circumference; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; FBS – fasting blood glucose; DBP – diastolic blood pressure; SBP – systolic blood pressure; BMI – body mass index. Values are expressed as number, median (Q1, Q3) and percentage. *According to the non-normal distribution of data with the Kolmogorov-Smirnov test, non-parametric tests were used. **Diabetes was diagnosed from the medical history, treatment with diabetic drugs or high blood sugar (FBS \geq 126). ***Hypertension was diagnosed from the medical history and treatment with blood pressure drugs. ****Heart disease was diagnosed from the medical history and treatment with heart disease medications. *****Based on the results of the Beck Depression Inventory (BDI).

BDI scores were significantly reduced in the crocin group ($p = 0.009$) but not in the placebo group ($p > 0.05$). However, the difference between the 2 groups in terms of the magnitude of the changes in BDI scores did not reach statistical significance ($p = 0.09$).

There was no significant association between changes in serum PAB values and the severity of depression. The magnitude of changes in PAB values was comparable between the subgroups with and without improvement in their BDI scores in both the crocin group and the placebo group ($p > 0.05$) (Table 3).

Discussion

The results of the present study showed that at a dose of 30 mg per day for 8 weeks, crocin was associated with a reduction in the degree of depressive symptoms in subjects with MetS. But no association was found between

the reduction in the degree of depression and the reduction of serum PAB.

Some previous animal studies have shown that saffron had a much greater antidepressant effect than a placebo; a 2004 study by Hosseinzadeh et al. found that this effect occurs through inhibition of the uptake of dopamine, norepinephrine and serotonin by saffranal and crocin, components of saffron.^{19,24} Also, some human clinical trials have compared the antidepressant effect of saffron on mice with standard medications, including imipramine and fluoxetine, and found that saffron can be as effective as standard medications in treating depression.^{25,26} In 2010 Wang et al. found that the antidepressant effect of extract of stigmas of saffron on mice is associated with the presence of crocin.²⁷

As noted earlier, studies have confirmed that MetS is associated with depression and that oxidative stress is implicated in the etiology of both depression and metabolic syndrome.^{14,15} The antidepressant mechanisms of saffron and its components are not still clear. In vitro and animal studies have shown the effectiveness of crocin in reducing depression, as well as its anti-oxidant properties.¹⁹ Therefore, crocin may be effective in treating both depression and oxidative stress in patients with Mets.

As far as the authors are aware, no study has previously been published about the effect of crocin on depression in human subjects. In 2011 Shemshian et al. conducted a study involving saffron and the BDI questionnaire.²¹ They assessed the effect of 100 mg of saffron per day for 12 weeks, compar-

ing it with a placebo on 60 patients with depression and anxiety. They found that saffron significantly reduced the BDI scores of depression in the patients, and concluded that saffron has a therapeutic antidepressant effect on patients with a clinical diagnosis of depression. The present study, on the other hand, assessed the effect of crocin on the symptoms of depression in subjects with MetS who have a mild to moderate degree of depression according to the BDI scale. Shemshian et al. used 100 mg saffron per day and the present study used 30 mg of crocin per day. Crocin comprises 10% of the dry weight of saffron, so the crocin dose in the present study was 3 times higher than in their study. However, in the study by Shemshian et al. there were other active components of saffron in addition to crocin.

The present study found no association between the reduction in the degree of depression and the serum PAB. This means that the results of this study did not support the theory that anti-oxidant action of crocin is involved in reducing the symptoms of depression in subjects with

Table 2. Comparison of changes in the degree of depression in the 2 groups

Study group and statistical test	Degree of depression* median (Q1–Q3) Week 0	Degree of depression* median (Q1–Q3) Week 8	Reduction in the degree of depression n (%)	Wilcoxon test (2-tailed p-value)
Crocin group (n = 16)	2.5 (2–3)	2 (1–2.75)	11 (68.8%)	p = 0.005
Placebo group (n = 17)	2 (2–3)	2 (2–3)	5 (29.4%)	p > 0.05
Mann-Whitney test for changes in the degree of depression in the 2 groups	p = 0.013 (2-tailed p-value)			

*The degree of depression based on the results of the Beck Depression Inventory (BDI) as follows: degree 1 – minimal depression (scores 0–9); degree 2 – mild depression (scores 10–18); degree 3 – moderate depression (scores 19–29) and degree 4 – severe depression (scores 30–63).

Table 3. Serum PAB changes in relation to reductions in the degree of depression

The study groups	Reduction in the degree of depression (n %)	PAB changes median (Q1, Q3)
Crocin group (n = 16)	reduction (n = 11, 68.8%)	-17.7 (-51.9, 5.2)
	no reduction (n = 5, 31.2%)	-4.9 (-22.31, 8.98)
Placebo group (n = 17)	reduction (n = 5, 29.4%)	-15.9 (-23.9, 9.6)
	no reduction (n = 12, 70.6%)	-6.82 (-34.3, 35.7)
Mann-Whitney test for the relation between changes in depression and PAB [†]	ns*	
Spearman correlation for changes in depression and PAB in the 2 groups	ns*	

*ns – not significant (p > 0.05); [†]In this Mann-Whitney test, reduction in the degree of depression (as two variables: 1 – no reduction, 2 – reduction) was the grouping variable, and change in serum PAB was the test variable.

MetS. It is likely that the main antidepressant mechanism of crocin is preventing the uptake of the neurotransmitters such as dopamine, norepinephrine and serotonin, as previous evidence has suggested, but this needs to be further explored in future clinical studies.

The main limitation of this study is that it included subjects who did not have a clinical diagnosis of depression, because it was a substudy of research that was not primarily designed to assess the impact of crocin on the participants' psychological status.²⁰ Other limitations include the small sample size, the evaluation of the effects of only 1 dosage (30 mg per day), and the relatively short duration of the treatment and follow-up. All of these limitations need to be addressed in future studies.

Conclusions

The results of this study showed that supplementation with crocin at a daily dose of 30 mg for 8 weeks could reduce the symptoms of depression in subjects with MetS, an effect that appears to be independent of changes in plasma PAB status.

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