Avicenna Journal of Phytomedicine (AJP)

Short communication

Effect of crocin supplementation on anthropometric parameters and symptom severity in clozapine-treated schizophrenia: A randomized controlled trial

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Article history:
Received: Oct 27, 2025
Received in revised form: May 18, 2026
Accepted: Jun 16, 2026
Epub ahead of print

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Keywords:
Schizophrenia
Clozapine
Crocin
Anthropometric parameters
Body mass index
Symptoms of schizophrenia

Abstract

Objective: Clozapine is the treatment of choice for individuals with treatment-resistant schizophrenia but its use is associated with weight gain and increased cardiovascular risk. Crocin is a bioactive carotenoid and it exhibited antioxidant and anti-inflammatory characteristics and efficacy against metabolic and/or psychiatric disorders. This study explored the effects of crocin on anthropometric parameters and symptom severity in clozapine-treated schizophrenia patients.

Materials and methods: Participants were randomly assigned to receive either crocin (30 mg/day) or placebo for 8 weeks in addition to their routine treatments. Primary outcome measures assessed were changes in body weight, BMI, and waist circumference and secondary outcome included changes in symptom severity assessed through the course of the study using the Positive and Negative Syndrome Scale (PANSS). Data collection was done at baseline and at weeks 4 and 8.

Results: Analysis of changes from baseline to week 8 revealed no statistically significant effect for crocin on weight or body mass index (BMI). However, crocin significantly changed PANSS subscale scores (positive and general psychopathology) compared to placebo. Crocin did not produce serious adverse effects.

Conclusion: While crocin caused significant psychiatric improvements, it could not significantly improve anthropometric measures in schizophrenia patients receiving clozapine.

Please cite this paper as:
Moradzadeh M, Ghorani V, Zibaei A, Ghayour-Mobarhan M, Azimzadeh Tehrani N, Rezaee R, Eslamzadeh M. Effect of crocin supplementation on anthropometric parameters and symptom severity in clozapine-treated schizophrenia: A randomized controlled trial.Avicenna J Phytomed, 2026

Introduction

Schizophrenia is a chronic and severe mental illness that is estimated to affect 0.32% of the population worldwide, approximately 24 million people globally (IoHMa 2021) . In Iran, a prevalence of 0.89% for schizophrenia was reported (Hemmati et al. 2022) . Schizophrenia affects perception, thought, and behaviors, and it results in significant disability and a lowered life expectancy of 15 to 20 years compared to the general population (Laursen, Nordentoft and Mortensen 2014; Olfson et al. 2015). The leading cause of this early death is cardiovascular disease attributable to metabolic syndrome which includes conditions such as abdominal obesity, high blood pressure, dyslipidemia, and hyperglycemia (Salari et al. 2024). Metabolic disturbances are common in people with schizophrenia, with research suggesting 41.3% of individuals with schizophrenia develop metabolic syndrome, a rate higher than the general population (Kane et al. 1988).

Among antipsychotics used for treatment for schizophrenia, clozapine is associated with the most positive outcome in treatment-resistant schizophrenia (Sadock 2015). Clozapine is an antagonist of dopamine D2 and serotonin 5HT2A receptors and reduces psychotic symptoms with potentially limited extrapyramidal side effects (Yuen et al. 2021). Clozapine adverse effects include severe metabolic effects such as weight gain, dyslipidemia, hyperglycemia, and metabolic syndrome, affecting 50-60% of clozapine-treated patients (Dayabandara et al. 2017; Hurley et al. 2023). These side effects increase the risk for type 2 diabetes and cardiovascular disease, negatively impacting medication adherence and adding to the overall disease burden (Dastkhosh et al. 2024). The current available treatments including lifestyle change and medications such as metformin, have shown some effectiveness but do not largely alleviate the metabolic burden (Jarskog et al. 2013).

It has been indicated that nearly 80% of Asian and African populations consider herbal treatments for primary health care and as per the US National Health and Nutrition Examination Survey (2003-2006), one fifth of adults consume supplements that have at least a botanical component. Nevertheless, safety assessments are required prior to consideration of the use of naturally occurring phytoconstituents as a disease treatment (Latif and Nawaz 2025; Tsatsakis et al. 2021)

Crocin, a major bioactive constituent of saffron (*Crocus sativus*), has long been used in traditional medicine for its pharmacological properties such as antioxidant and anti-inflammatory activity, and potential regulatory effects on metabolic abnormalities (Hashemzaei et al. 2020; Rezaee et al. 2013). Recent clinical trials have shown that crocin improves lipid profile and decreases oxidative stress in type 2 diabetes patients, indicating its potential against metabolic disorders (Pitsikas 2021). Crocin has also shown promise for the treatment of psychiatric disorders like depression and anxiety (Fadai et al. 2014; Ghaderi et al. 2020).

Since no clinical trial has so far assessed the effects of crocin supplementation on clozapine-associated weight gain and other metabolic disturbances, the current study examined crocin effects on anthropometric parameters (body weight, body mass index (BMI) and waist circumference) and psychologic symptoms (positive, negative, and general psychopathology as measured by the Positive and Negative Syndrome Scale (PANSS)), in clozapine-receiving schizophrenia patients.

Materials and Methods

Study Design and Setting

This study was designed as a two-arm, parallel-group, randomized, double-blind, placebo-controlled clinical trial and conducted at the Hejazi Educational and Research Hospital, an inpatient and

outpatient psychiatric center affiliated with Mashhad University of Medical Sciences, Mashhad, Iran. Recruitment and intervention took place between October 2022 and September 2023 with each participant undergoing an 8-week intervention. Follow-ups were done at baseline, week 4, and week 8.

Study population

The flow of the participants through the trial, including enrollment, randomization, follow-up, and analysis, is illustrated in Figure 1.

Participating subjects were male and female adults aged 20-60 years who were diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (Tandon 2014).

The inclusion criteria were: (1) taking regular doses of clozapine for at least 1 month prior to enrolment, (2) having Body Mass Index (BMI) greater than 25 kg/m², (3) being 20-60 years old and (4) signing informed consent at the time of recruitment, by either the participant or a legal guardian. The exclusion criteria were: (1) poor adherence to study medication (i.e. using less than 80% of the total dosage), (2) having significant adverse effects necessitating discontinuation, (3) changing the eating behavior due to acute stress, or (4) changing the clozapine dosage during the study.

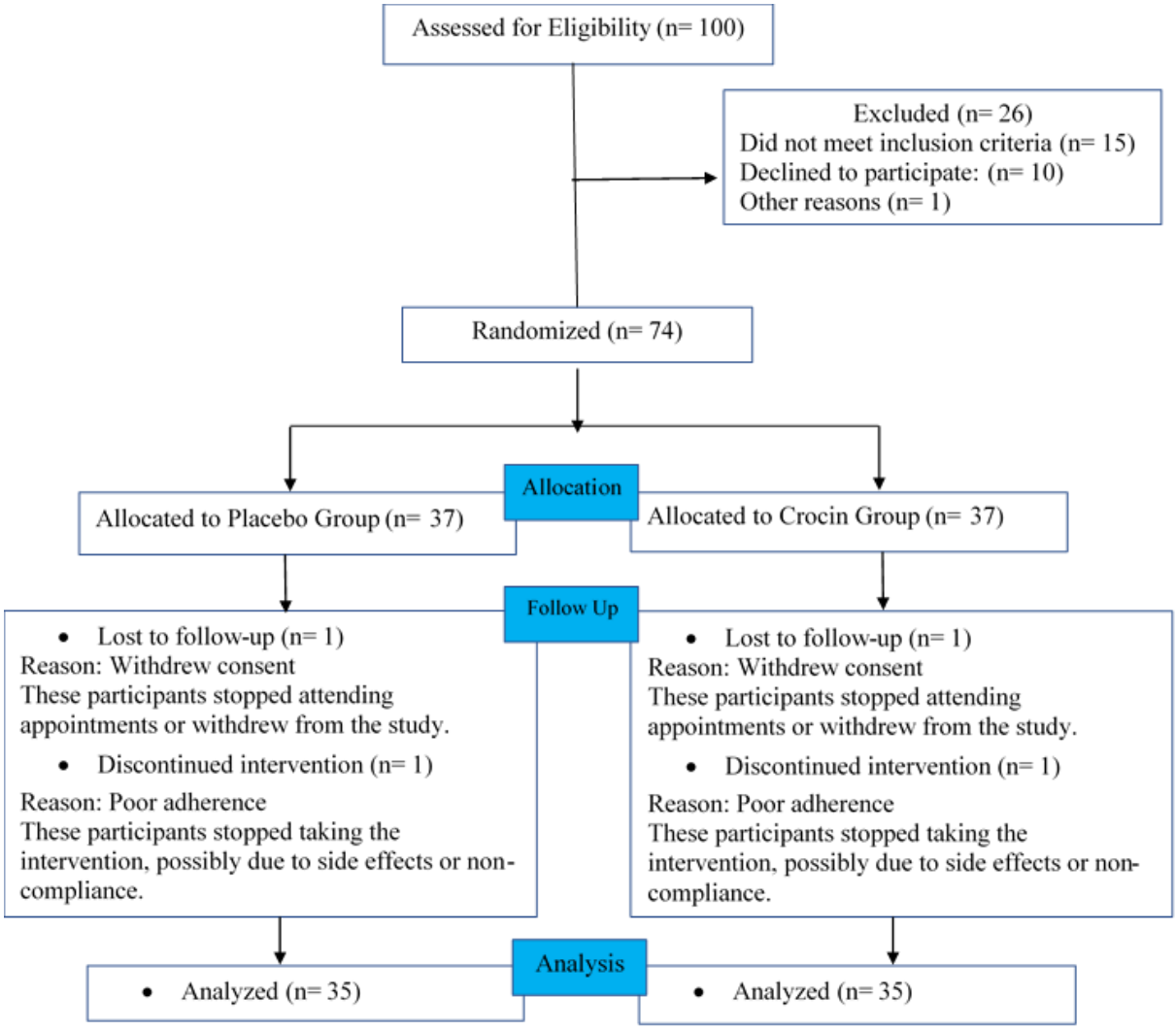

Figure 2. CONSORT Flow of the present trial.

Ethical considerations

The study protocol (Research Project No. 4001268) was approved by the Institutional Review Board of Mashhad University of Medical Sciences (Ethics Committee Code: IR.MUMS.MEDICAL.REC.1401.083). Signed written informed consent was obtained from all participants or their legal guardians. The trial was registered with the Iranian Registry of Clinical Trials (IRCT20211202053250N2).

Intervention and control

Intervention group

Participants received oral tablets containing 15 mg of crocin (Provided by the School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran), twice daily (total 30 mg/day), for 8 weeks.

Control group

Participants received placebo tablets (identical in appearance to the crocin tablets), twice daily, for 8 weeks. Both groups continued standard clozapine treatment as prescribed.

Randomization and allocation concealment

Participants were randomly allocated in a 1:1 ratio to the crocin or placebo group using a computer-generated random number sequence. Blinding was maintained for participants and care providers, while allocation concealment was ensured using sequentially numbered, sealed, opaque envelopes which were opened only at enrollment by a staff member not involved in the study.

Data collection and outcome measures

Collected data included: (1) demographic information (age and sex), (2) anthropometric measures (weight determined via calibrated digital scale, height via stadiometer, waist circumference via non-stretchable tape at the midpoint between the lower rib and iliac crest, and BMI calculated in kg/m²), and (3) psychiatric symptom severity determined via the Positive and Negative Syndrome Scale (PANSS), administered by trained raters with inter-rater reliability checks. In this trial, body weight, BMI and waist circumference (the primary outcomes) and PANSS subscale scores (the secondary outcome) were reassessed before initiation of the intervention and at weeks 4 and 8. All patients were followed-up on a weekly basis by phone call and any possible adverse drug reaction was recorded during the study period.

Instruments

PANSS subscale scores (positive, negative, and general psychopathology), were determined using a 30-item, 1-7 Likert scale questionnaire, by trained psychiatrists or psychologists at weeks 4 and 8 and compared with the baseline data. The Persian PANSS has shown good reliability (Cronbach's $\alpha = 0.77–0.80$) and acceptable validity (six-factor structure, 47.1% discriminant accuracy) in previous studies done on Iranian schizophrenia subjects (Ghamari Givi, Moulavi and Heshmati 2010; Sarafraz, Mahmoudi Tabar and Pourshams 2025).

Dietary intake monitoring

A nutrition specialist monitored the nutritional regimen of both groups to minimize dietary variations as a potential confounder.

Sample size calculation

The sample size was calculated to detect a 30% reduction in weight gain frequency (expected 55% in the placebo group as suggested by Manu et al. (Manu et al. 2015) with crocin, using alpha=0.05 and 80% power. This required 34 participants per group, increased to 37 per group to account for a 10% dropout rate.

Statistical analysis

Statistical analysis was performed using SPSS version 26. Descriptive statistics are

shown as median and interquartile range for non-parametrically distributed data. To compare the crocin and placebo groups at baseline, continuous variables (e.g. age) were analyzed using Independent-sample T-test, and nominal variables (e.g. gender) were analyzed using Chi-square test. Within-group comparisons at baseline, week 4, and week 8 were made using Friedman test and Repeated measure test, and Independent-sample T-test and Mann-Whitney U test were used for making comparisons between the two groups. A p-value <0.05 was considered significant.

Results

Characteristics of participants

Demographic characteristics of the subjects are displayed in Table 1. The average age and sex distribution did not differ significantly between the two groups.

Effect of crocin on anthropometric measures

Table 2 presents the mean and standard deviations for weight, BMI, and waist circumference at baseline, week 4, and week 8 for both groups. The anthropometric measures did not show significant differences between the two groups at baseline.

Anthropometric measurements in each of the crocin and placebo groups showed only slight changes during the 8-week intervention period, according to within-group analyses. In the crocin group, minimal changes in weight, BMI and waist circumference from baseline to week 8 were observed and these changes were not statistically significant except for waist circumference, suggesting that crocin could not influence these parameters. From baseline to week 8, the crocin group average weight increased by 0.81±1.89 kg, BMI increased by 0.27±0.66 kg/m^2, and waist circumference increased by 1.57±3.06 cm. Comparably, during the same time period, the placebo group average weight decreased by 1.37±3.23 kg, BMI declined by 0.48±1.07 kg/m^2, and waist circumference decreased by 1.49±10 cm. Importantly, the between-group comparison of the changes in weight and BMI were statistically significantly different between the groups (p<0.001 for both cases).

Table 1. Demographic and clinical characteristic of the patients in the two groups

Variables		Groups		p-value
		Placebo group (n=35)	Crocin group (n=35)	
Sex, N (%)	Male	26 (74.3%)	24 (68.6%)	0.792 [a]
	Female	9 (25.7%)	11 (31.4%)	
Age, Mean±SD		48.46 ± 7.48	50.86± 8.72	0.221 [b]

[a] Pearson Chi-Square. [b] Independent- sample T-test

Table 2. Effect of crocin on weight, BMI, and waist circumference at baseline, week 4, and week 8 for the crocin and placebo groups

Measure	Group	Baseline	Week 4	Week 8	p-value*	Mean change [a]	p-value#
Weight (kg)	Crocin	76.79± 13.39	77.06 ± 13.63	77.60 ± 13.68	ns	0.81±1.89	0.001 [a]
	Placebo	80.77 ± 11.71	80.89 ± 11.15	79.40 ± 11.49	<0.05	−1.37±3.23	
BMI (kg/m²)	Crocin	26.49 ± 2.77	26.58 ± 2.83	26.76 ± 2.78	ns	0.27±0.66	<0.001 [a]
	Placebo	27.69 ± 3.44	27.72 ± 3.14	27.20 ± 3.29	<0.05	−0.48±1.07	
Waist Circumference (cm)	Crocin	105.03 ± 8.44	104.57 ± 8.48	106.60 ± 8.20	<0.05	1.57±3.06	0.077 [b]
	Placebo	104.94 ± 7.91	103.09 ± 8.14	103.46 ± 6.95	<0.05	−1.49±10	

Values are presented as mean ± SD.*Within-group statistical comparisons were performed using Repeated measure test.[a] Change score (score at week 8 minus baseline value). [#]Comparison between the crocin and placebo groups was made by Independent- sample T-test [a] and Mann-Whitney U test [b].ns: non-significant

Effect of crocin on schizophrenia symptoms

Crocin supplementation greatly improved schizophrenia symptoms across all three PANSS axes: Positive symptoms (e.g. hallucinations), negative symptoms (e.g. social withdrawal), and general psychopathology (e.g. anxiety). The mean scores for these subscales at baseline, week 4, and week 8 for the crocin and placebo groups are shown and compared in Table 3. There was a significant difference in positive and general symptoms between the two groups at baseline ($p<0.05$ for both cases), but baseline values for negative symptoms did not vary significantly between the groups.

Table 3 . PANSS subscale scores for the crocin and placebo groups at baseline, week 4, and week 8

Subscale	Group	Baseline	Week 4	Week 8	p-value*
Positive Symptoms	Crocin	24.0 (18.00, 27.00)[#]	18.0 (16.00, 22.00)	15.0 (13.00, 20.00)	<0.001
	Placebo	20.0 (17.00, 23.00)	18.0 (14.00, 21.00)	16.0 (13.00, 20.00)	0.007
Negative Symptoms	Crocin	21.0 (19.00, 25.00)	21.0 (17.00, 23.00)	16.0 (12.00, 19.00)	<0.001
	Placebo	22.0 (18.00, 26.00)	19.0 (15.00, 24.00)	16.0 (13.00, 18.00)	0.001
General	Crocin	52.0 (47.00, 56.00) [#]	46.5 (40.00, 52.00)	37.0 (34.00, 41.50)	<0.001
Psychopathology	Placebo	47.0 (38.00, 53.00)	48.0 (37.00, 54.00)	39.0 (34.00, 46.00)	0.005

Values are presented as Median (25 and 75 quartiles).*Within-group statistical comparisons were performed using Friedman test.[#] $p<0.05$ shows significant differences between the crocin and placebo groups at baseline, as assessed by Mann-Whitney U test.

Analysis of trends of positive, negative, and general symptoms revealed significant changes from baseline to week 8 in both groups ($p\leq0.001$ for all cases). Although all symptom domains demonstrated a declining trend, the reduction was more substantial in the crocin group.

The between-group comparison of the changes in PANSS subscale scores (score at week 8 minus baseline value), using the Mann-Whitney U test, revealed a statistically significant difference favoring the crocin group ($p<0.05$ to $p<0.01$).

For each PANSS subscale, the results of comparisons made using Mann-Whitney U test were as follows:

Positive symptoms: The score at week 8 was significantly lower than that of the baseline in the crocin group ($p<0.001$), and the reduction was greater compared to the placebo group ($p< 0.05$).

Negative symptoms: The score at week 8 was significantly lower than that of the baseline in the crocin group ($p<0.001$), and the reduction was greater compared to the placebo group that was not statistically significant ($p=902$).

General psychopathology: The score at week 8 was significantly lower than that of the baseline in the crocin group ($p<0.001$), and the reduction was greater compared to the placebo group ($p<0.01$).

Discussion

Clozapine treatment is likely to be associated with higher metabolic adverse events compared to other antipsychotics, possibly through increased appetite or changes in lipids metabolism with direct effects on adipose tissue (Yuen et al. 2021). Previous research on saffron and its constituents (specifically crocin) has shown their beneficial effects on metabolic parameters. In a clinical study, patients diagnosed with schizophrenia, who were undergoing treatment with olanzapine, received a carefully prepared aqueous extract of *C. sativus* (1 g daily) over 84 days; the intervention successfully curbed the emergence of metabolic syndrome in these individuals (Fadai et al. 2014). Likewise, *C. sativus* substantially reduced BMI and waist circumference in patients with coronary artery disease (Pourmasoumi et al. 2019). However, in our study, crocin supplementation could not produce

ameliorative effects on weight, BMI, or waist circumference in clozapine-treated participants after the 8-week intervention. Nevertheless, increases in weight, BMI and waist circumference observed in the crocin group, were not statistically significant. On the other hand, these variables in the control group showed a non-linear pattern, with initial increases followed by a decrease at week 8, suggesting temporal fluctuation. Therefore, these findings do not support clear beneficial or adverse effect of crocin and potentially are more likely attributable to the known metabolic effect of clozapine and other uncontrolled factors.

Crocin as a bioactive carotenoid, possesses antioxidant and anti-inflammatory properties and has the ability to reduce oxidative stress and promote satiety. In a randomized clinical trial, crocin supplementation for 12 weeks at a dose of 30 mg/day improved lipid profiles by decreasing triglyceride levels and total oxidative stress in type 2 diabetic patients, suggesting its value in reducing dyslipidemia and oxidative stress (Dastkhosh et al. 2024). Likewise, among type 2 diabetes patients, crocin (15 mg twice daily for 12 weeks) increased glycemic control, reduced fasting glucose, hemoglobin A1c, and insulin resistance and enhanced insulin sensitivity, indicating its efficacy in improving glucose utilization (Behrouz et al. 2020). Moreover, crocin administered to streptozotocin-diabetic rats, could improve insulin sensitivity and lipids profiles. It is likely that these benefits arose from greater insulin sensitization of insulin receptors and supports crocin potential to improve dyslipidemia and hyperglycemia (Shirali, Zahra Bathaie and Nakhjavani 2013). Studies have also examined whether crocin may alleviate adverse metabolic events associated with antipsychotic treatment. For example, in olanzapine-receiving schizophrenia patients, crocin significantly reduced weight gain and improved lipids (Fadai et al. 2014).

Limited research has been conducted examining the effect of crocin on schizophrenia in humans, but crocin has demonstrated beneficial effects on a variety of other psychological conditions. Randomized controlled trials have indicated that crocin was effective in reducing symptoms of anxiety and depression (Mazidi et al. 2016; Talaei et al. 2015).

Our findings demonstrate that crocin supplementation resulted in significant improvements across all three PANSS axes, with reductions in each subscale being statistically greater than those observed in the placebo group. Participants in the crocin group showed significant improvement in positive and negative symptoms, and general psychopathology as demonstrated by a significant decrease in PANSS scores from baseline to week 8. Also, between-group comparisons indicate that reductions in the crocin group were greater than those observed for the placebo group for each subscale. Findings suggest that crocin may be an effective adjunct treatment to ameliorate psychiatric symptoms in patients with clozapine-treated schizophrenia. These findings are similar to earlier research showing some benefit for crocin use in patients with psychiatric illnesses.

For instance, crocin improved cognitive and negative symptoms in people with schizophrenia at doses of 15-30 mg/kg (Pitsikas 2021). In the current study, the crocin group had higher baseline PANSS scores for positive symptoms and general psychopathology but at week-8 follow-up, the crocin group outcomes were comparable to or better than those of the control group. This suggests crocin promising therapeutic potential in reducing schizophrenia symptoms. Crocin antioxidant and neuroprotective effects likely contributed to these benefits as crocin alleviates oxidative stress and reduces the levels of reactive oxygen species (ROS) in the body by promoting higher levels of certain antioxidant enzymes such as

superoxide dismutase. Oxidative stress has been proposed to be a central factor in the pathophysiology of schizophrenia, and research has shown elevated ROS levels and a marked decrease in antioxidant defenses in affected patients (Cuenod et al. 2022). Therefore, crocin might be considered a potential therapeutic for treating symptoms of schizophrenia; however, larger clinical trials conducted over longer intervention and/or follow-up periods are required to verify the present findings.

There are several limitations to consider when interpreting these results. The study's dosage of 30 mg/day of crocin and treatment duration of 8 weeks may have been insufficient. A previous study on *C. sativus* (Fadai et al. 2014) used the same dose but extended the duration to 12 weeks. Furthermore, higher crocin doses might be required to combat clozapine potent effects on weight and metabolic markers. The single-center nature of the study limits the generalizability of the findings. Variables such as physical activity or stress were not controlled, and these may have contributed to the overall results. Another limitation was that complete records of clozapine dose and duration of treatment history -before enrollment- were not available for all participants. Thus, results presented in this work should be interpreted with caution and further trials are required to assess these findings.

In the present trial, crocin produced a significant decrease in PANSS scores and this provides ground for further assessments for possible application of this bioactive compound as an adjunct therapeutic for improving psychiatric outcomes in schizophrenia patients receiving clozapine.

This study indicates that in schizophrenia patients receiving clozapine, 8 weeks of crocin supplementation could not produce a statistically significant effect on weight gain or BMI but effectively alleviated PANSS scores compared to placebo. These results should be considered with caution and it is suggested that in the future, larger clinical trials over longer intervention and/or follow-up periods be conducted to verify the present findings.

Acknowledgment

Authors are thankful to vice chancellor for research of Mashhad University of Medical Sciences for financial support of the present trial (Research Project No. 4001268 and Ethics Committee Approval No. IR.MUMS.MEDICAL.REC.1401.083).
The content of this article has been presented as a specialty degree in psychiatry by Mahboobeh Moradzadeh.
The authors would like to thank the participants for their cooperation and the staff of Hejazi Hospital for their assistance during the study.

Conflicts of interest

The authors had no competing interests.

Funding

Vice chancellor for research of Mashhad University of Medical Sciences provided the financial support of the present trial (Research Project No. 4001268).

Code of Ethics

Mashhad University of Medical Sciences Ethics Committee approved the present study (No. IR.MUMS.MEDICAL.REC.1401.083).

Authors' Contributions

Mahboubeh Eslamzadeh and Ramin Rezaee: Supervised and contributed to study design and methodology, and review of the manuscript.
Majid Ghayour-Mobarhan: Provided support on nutritional aspects of the study, and reviewed the manuscript.
Vahideh Ghorani: Provided support on study design, data analysis, and final manuscript editing.

Mahboobeh Moradzadeh: Contributed to conceptualization, data collection, and writing of the manuscript.
Alireza Zibaei and Negar Azimzadeh Tehrani: Contributed to literature review, data analysis and writing of the manuscript.

Abbreviations

PANSS: Positive and Negative Syndrome Scale
BMI: Body Mass Index
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
IRCT: Iranian Registry of Clinical Trials
SPSS: Statistical Package for the Social Sciences

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