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Efficacy of Saffron Capsules on Binge Eating Episodes, Appetite and Body Mass Index of Individuals with Binge Eating Disorder: A 12-Week Randomized Clinical Trial

Sasan Amiri[1], Seyed-Ali Mostafavi[2], Ahmad Ali Noorbala[1], Ariana Karkhaneh Yousefi[2], Shahin Akhondzadeh[2*]

Abstract

Objective: We aimed to assess the efficacy of saffron versus placebo on binge eating severity, appetite, and body mass index (BMI) in adults diagnosed with binge eating disorder (BED).
Method: This was a 12-week randomized, double-blind, placebo-controlled trial with parallel design. We randomized 59 participants with confirmed diagnoses of BED according to DSM-5 criteria to receive either saffron extract (15 mg per capsule twice daily; total daily dose 30 mg; n = 30) or placebo (15 mg starch per capsule twice daily; n = 29). We assessed binge eating episodes (daily diary), appetite (visual analogue scale [VAS]), BMI, and macronutrient intake (3-day food records) before and after the trial. We analyzed the data using the intention-to-treat (ITT) approach and paired t-tests/Wilcoxon tests for within-group changes and independent t-tests/Mann-Whitney U tests for between-group differences. Furthermore, we used analysis of covariance (ANCOVA) with the primary outcome as the dependent variable and key baseline variables as covariates to compare endpoint outcomes between groups.
Results: We detected significant reductions in the saffron group compared with the placebo group in binge eating severity (mean difference: −1.16 ± 0.25; P ≤ 0.001; Cohen's d = −1.30), Appetite VAS scores (−3.34 ± 0.56; P ≤ 0.001; Cohen's d = −1.76), Calorie intake (−448 ± 113 kcal/day; P ≤ 0.001; Cohen's d = −1.03), and Fat intake (−21.45 ± 5.10 g/day; P ≤ 0.001; Cohen's d = −1.09). Furthermore, the saffron group showed a significant decrease in mean difference of BMI (−0.61 ± 0.45 kg/m²; P = 0.006; Cohen's d = −0.43). ANCOVA results revealed that the adjusted treatment effect was -1.10 (95% CI: -1.60 to -0.60, P < 0.001).
Conclusion: Saffron supplementation significantly decreases the core symptoms of BED, reduces appetite and caloric intake, and modestly lowers BMI. Saffron capsules could be considered a safe and efficient supplement for people undergoing BED treatment.

Key words: *Appetite; Body Mass Index(BMI); Binge-Eating Disorder; Dietary Intake; Randomized Controlled Trial; Saffron*

1. Psycosomatic Medicine Research Center, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.
2. Psychiatry and Psychology Research Center, Tehran University of Medical Sciences, Tehran, Iran.

***Corresponding Author:**
3. Address: Psychiatry and Psychology Research Center, Tehran University of Medical Sciences, Tehran, Iran, Postal Code:1333715914
Tel: 98-21 55412222, Fax: 98-21 55419113, Email: s.akhond@sina.tums.ac.ir

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Binge Eating Disorder (BED) is the most commonly diagnosed eating disorder in clinical settings. It is also the most predominant type of eating disorder, with an estimated lifetime prevalence of 1-3% in women and less than 1% in men, while studies suggest a point prevalence of about 1 in 200 women and approximately 1 in 400 men (1, 2).

The fundamental criteria in diagnosing BED involve the occurrence of a binge eating episode. In general, according to the DSM-5-TR (current diagnostic framework), two key elements must be present for an eating episode to be diagnosed as a binge: (a) consumption of an objectively large quantity of food within a specific timeframe, and (b) the inability to control eating during this episode. The individual must experience the symptoms at least once weekly over a three-month period or longer. In contrast to bulimia nervosa, individuals with BED typically do not engage in compensatory behaviors following binge eating episodes (3, 4).

Prevalence of obesity and overweight is high among individuals with BED, putting these individuals at risk for weight-related health complications. However, compared to other eating disorders, little is known about the clinical management of BED. Much of the research on BED treatment has focused on behavioral interventions targeting binge eating (5). Nonetheless, a large percentage of patients with BED who are overweight or obese may require additional treatment to achieve a healthier body weight, although clinicians tend to agree that binge eating should be addressed before weight reduction is attempted. Additional studies on binge eating frequency and subjects' obesity grade are needed (6).

Among available interventions, psychotherapies—especially cognitive-behavioral therapy (CBT)—have been widely evaluated for the treatment of BED. Investigators report that approximately half of patients do not respond to CBT (5). Research has identified several pharmacological options that may reduce symptoms in many BED patients. Particularly, some antidepressants (selective serotonin reuptake inhibitors and tricyclic antidepressants) have demonstrated effectiveness compared with placebo in reducing binge frequency, though they typically do not contribute to weight reduction. Topiramate, an anticonvulsant medication, has shown promise, as it appears to both decrease binge eating behaviors and support weight loss. Medications designed primarily for weight management have received limited study in BED populations, with orlistat showing some effect on weight but minimal impact on binge behaviors. Researchers have explored other appetite-suppressing medications including certain stimulants for this condition. More recently, the stimulant medication lisdexamfetamine has received regulatory approval for short-term BED treatment. However, most pharmacological trials have been limited to brief examinations of immediate effects rather than long-term outcomes (7).

Existing medications for BED, such as topiramate and sibutramine, have low compliance rates due to adverse effects, safety concerns, and resistance to treatment (8). Although one antidepressant has received regulatory approval for a similar eating disorder (bulimia nervosa), evidence supporting its efficacy in BED remains inconsistent. Despite the consequences of BED, treatment options with few side effects are not currently available. BED treatment should not rely exclusively on pharmacological interventions, such as serotonergic medications that only aim to reduce food intake, given the urgent need for innovative therapies for both bulimia nervosa and BED that minimize adverse side effects (9).

Studies suggest that stress and negative affect are possible triggers of binge eating; hence, an agent that reduces these factors could decrease binge episodes in subjects with BED (10). Saffron is the dried stigma of the flower Crocus sativus L. It has been used in traditional medicine as an antidepressant and is known to have satiety-enhancing effects. research has noted its potential appetite-regulating effects. These beneficial properties likely stem from several compounds in saffron, including crocetin and safranal. Research suggests that these compounds have strong antioxidant properties that may help protect against oxidative stress and inflammation. Some research indicates that saffron may influence mood through its potential effects on brain chemistry, possibly by modulating neurotransmitter activity in a manner similar to some antidepressant mechanisms. Preliminary animal studies suggest it might influence serotonin pathways by potentially slowing its reabsorption, though additional human research is necessary to confirm these findings (11).

The growing obesity epidemic is a global public health issue due to its associated health complications and negative impacts on quality of life. BED is the most prevalent co-occurring mental health disorder in individuals with obesity. Based on previous findings, we hypothesized that saffron capsules may decrease binge episodes and appetite through mood regulation and, over time, may decrease body weight and obesity in subjects with BED. Modulating mood and abnormal food intake might subsequently contribute to better body weight control and decreased BMI. Hence, we designed this study to determine the efficacy of saffron capsules on binge eating episodes, appetite and BMI in subjects with BED in a double-blind placebo-controlled randomized clinical trial.

Materials and Methods

Study design and procedure

This was a randomized, double-blind, placebo-controlled study with parallel design. The study protocol was registered with Iranian registry for clinical trials: RCT RCT20090117001556N149. The study was conducted at

an eating disorder clinic. We described the study procedure and aims to potential participants and invited them to participate in the study. Volunteers then provided consent and underwent a semi-structured interview using the SCID-5 questionnaire, performed by a psychiatrist. Participants with confirmed diagnoses of BED according to the DSM-5 were randomly assigned to either the saffron group or the placebo group. The primary outcome of this study was binge eating episodes. During the trial period, participants recorded episodes of binge eating (consuming large amounts of food in less than two hours), feelings of lack of control over food consumption (inability to stop eating), the frequency of eating alone, the frequency of eating when not physically hungry, the frequency and intensity of guilt after binge eating, the frequency of feeling full after binge eating, and snacking in a daily diary. Weight and height were measured and BMI was calculated; furthermore, appetite was assessed using a visual analogue scale. Participants were trained to record everything they ate on a three-day food record sheet before and after the trial.

Sample size

Due to lack of studies on binge eating, the sample size was calculated to detect a 1.5 kg weight difference ($\mu 1-\mu 2 = 1.5$) between the saffron and placebo groups with a type I error rate of $\alpha = 0.05$ and a power of $1-\beta = 0.80$. According to a study by Gout *et al.* (31), the pooled standard deviation of weight in the saffron study was 1.44. Therefore, 15 participants in each group were considered sufficient. However, to increase the power of the study, sampling continued until 30 participants were enrolled in the saffron group and 29 in the placebo group, totaling 59 participants.

Inclusion and exclusion criteria

Individuals with a diagnosis of BED according to DSM-5 criteria (confirmed by the semi-structured interview SCID-5) were included. The exclusion criteria were: current or recent (within the past three months) medical treatment for weight loss or eating disorders; recent history of or active substance use disorder; diabetes mellitus; hypothyroidism; current participation in a weight reduction diet; strenuous physical activity (> three hours of intense exercise per week); medications or supplements affecting appetite and weight (including antidepressants, antipsychotics, corticosteroids, or weight loss supplements); psychiatric medications; history of bariatric surgery; a diagnosis of other eating disorders such as bulimia nervosa or anorexia nervosa; and known allergy or sensitivity to saffron.

Randomization, blinding and allocation concealment

The randomization sequence was computer-generated using Microsoft Excel 2016 with a simple randomization method. The allocation ratio was 1:1. The allocation was concealed, and the randomization list was kept secure. The randomization sequence was generated by an independent person who was not involved in the study conduct or data collection. The allocation sequence was concealed in sequentially numbered, opaque, sealed envelopes that were managed only by the study pharmacist responsible for intervention preparation. The medications (saffron and placebo) were kept blind, packaged identically, and coded by the manufacturer. The group allocation was concealed from the patients, researchers, and the trial statistician until the statistical analyses were completed. The saffron and placebo capsules were identical in appearance, size, weight, and color and were packaged in identical containers to maintain blinding. Participants were instructed to swallow the capsules without opening them, which minimized any potential taste differences. The patients and researchers were unaware of the assignment sequence to prevent selection bias.

Intervention

The saffron capsules (15 mg of standardized saffron extract per capsule) were taken twice daily (at breakfast and lunch), providing a total daily dose of 30 mg, and placebo capsules (15 mg of starch per capsule) were administered similarly at breakfast and lunch. Both saffron and placebo capsules were produced and packaged by the Green Plants of Life Co. Ltd. The saffron extract, branded as Saframood, was derived from the dried stigmas of Crocus sativus L. and was identified and standardized by the company's pharmacist. Quality control testing, including heavy metal analysis, microbial testing, and purity assessment, was conducted by the company. The placebo capsules contained 15 mg of starch and were identical in appearance to the saffron capsules. They were stored at room temperature (20-25°C) in light-resistant containers and taken twice a day, at breakfast and lunch.

Assessment intervals

The study duration was 12 weeks. Adherence to the study intervention was monitored through weekly phone calls and SMS reminders. In addition, at the final visit, we counted the used and unused capsules returned by participants. Patient assessments were performed at baseline and twelve weeks after the intervention began. Weight-related factors such as BMI, daily calorie intake, appetite, and number of binge-eating episodes were assessed before and after the study period in both groups to compare mean differences. Furthermore, patients reported the side effects they experienced during the study. These side effects were systematically recorded during the study using a researcher-made questionnaire.

Data analysis method

The data were gathered and entered into Excel, then exported to SPSS 18. First, the normality of the data was examined using the Kolmogorov–Smirnov and Shapiro-Wilk tests and assumptions were checked. In variables with normal distribution, the paired samples t-test and independent samples t-test were used. For variables in which normal distribution was not met, the Wilcoxon signed rank test and Mann-Whitney U-test were used. Furthermore, we performed an analysis of covariance (ANCOVA) adjusting for baseline values of the primary

outcome (binge eating severity at week 12) and key secondary outcomes (appetite, and BMI). The ANCOVA model included the treatment group as the independent variable and important baseline variables as covariates.

We used the intention-to-treat (ITT) approach for data analysis. We included all randomized participants in their originally assigned groups, regardless of adherence or dropout. Missing data were handled using multiple imputation, which incorporated baseline characteristics and observed outcome measurements to estimate plausible values for missing endpoints. To control for multiple testing, we applied the Benjamini-Hochberg false discovery rate (FDR) procedure to all p-values. FDR-adjusted q-values are reported alongside the original p-values, with an FDR threshold of 0.05 considered statistically significant.

Study tools

Scale: We used a calibrated Seca scale for accurate weight measurement in standard conditions.

Stadiometer: We used a non-stretch stadiometer for height measurement in standard conditions.

Appetite visual analogue scale: Visual analogue scales are commonly used in appetite studies. The Persian version of this tool was used alongside the Simplified Nutritional Appetite Questionnaire (SNAQ) and other eating questionnaires, and it showed strong correlation (concurrent validity) with them ($r = 0.7$, $P < 0.001$) (12).

Three-day food record form: Subjects were trained to record everything they ate during three randomly selected days (two working days and one holiday) at both baseline and endpoint. A registered nutritionist instructed them on the portion sizes of different foods and asked them to complete the food diary accordingly. Participants were instructed to estimate portion sizes using standardized household measures (cups, spoons, and common visual aids), which were then converted to grams using validated food composition reference tables. Participants were provided with a food record diary containing detailed instructions and examples. The nutritionist reviewed and double-checked the filled-in records to ensure completeness. We estimated the average daily dietary intake of total calories, carbohydrates, protein, fat, and sugar. This tool is validated and used in different studies (13).

Ethics

Before the study and sampling, ethics approval was obtained from the research ethics committee of Research Ethics Committees of Imam Khomeini Hospital Complex- Tehran University of Medical Sciences (Ethics code: IR.TUMS.IKHC.REC.1401.454). Furthermore, written informed consent was obtained from the participants. In the case of unwanted symptoms, patients were treated free of charge. The principles of the Declaration of Helsinki regarding clinical research on human subjects were observed.

Results

Fifty-nine participants were randomized (saffron: n = 30; placebo: n = 29). Of these, 50 participants completed the 12-week trial (saffron: n = 28; placebo: n = 22). All 59 randomized participants were included in the ITT analysis. Figure 1 shows the flow diagram of the study. The subjects were aged between 24 and 58 years (mean age: 38.5 ± 7.7). There were no significant differences between groups regarding the baseline variables (Table 1). Age, demographic characteristics, binge eating severity, appetite, BMI, or macronutrient intake were comparable between groups at baseline (all $P > 0.05$).

Compared with placebo, saffron supplementation significantly reduced binge eating episodes (mean change: −1.40 ± 1.06 vs. −0.23 ± 0.61; between-group difference: −1.16 ± 0.25; $P \leq 0.001$; Cohen's d = −1.30) (Table 2; Figures 2–3). No significant changes occurred within the placebo group ($P = 0.096$). A ≥ 50% reduction in binge eating episodes was achieved by 40% (12/30) of participants in the saffron group compared with 17% (5/29) in the placebo group ($P = 0.056$, Fisher's exact test).

In participants taking saffron capsules, appetite (VAS) decreased significantly compared with placebo (mean change: −3.12 ± 2.04 vs. −0.20 ± 1.71; between-group difference: −3.34 ± 0.56; $P \leq 0.001$; d = −1.76). Saffron also reduced dietary calorie intake (−426 ± 571 kcal vs. placebo: +22 ± 219 kcal; between-group difference: −448 ± 113 kcal; $P \leq 0.001$; d = −1.03). Reductions in fat (−13.98 ± 22.26 g vs. placebo: +7.47 ± 16.36 g; $P \leq 0.001$), sugar (−23.19 ± 52.20 g vs. +1.74 ± 33.07 g; $P = 0.039$), and carbohydrate intake ($P = 0.056$) were significant (Table 2). Changes in protein intake were not significant ($P = 0.125$). However, as a secondary outcome, BMI decreased significantly with saffron versus placebo (mean change: −0.62 ± 1.63 kg/m² vs. −0.09 ± 1.53 kg/m²; between-group difference: −0.61 ± 0.45; $p = 0.006$; d = −0.43) (Table 2).

An ANCOVA was conducted to examine the effect of treatment (saffron vs. placebo) on post-intervention binge eating severity, after controlling for baseline binge eating severity, BMI, and appetite. The overall model was statistically significant ($F(4,54) = 32.32$ $F(4,54) = 32.32$, $P < 0.001$) and accounted for a substantial portion of the variance in post-treatment scores ($R^2 = 0.705$, adjusted $R^2 = 0.684$). After adjusting for covariates, the saffron group demonstrated significantly lower post-treatment binge eating severity (Madj = 3.30, SE = 0.15, 95% CI [2.99, 3.60]) compared with the placebo group (Madj = 4.35, SE = 0.16S, 95% CI [4.04, 4.66]), $F(1,54) = 22.62$, $P < 0.001$, indicating a large treatment effect. Among the covariates, only baseline binge eating severity emerged as a significant predictor of post-treatment scores, $F(1,54) = 88.47$, $P < 0.001$, whereas baseline BMI ($P = 0.372$) and baseline appetite ($P = 0.609$) were not significantly associated with the outcome (Table 3).

ANCOVA analyses adjusting for important baseline variables, including binge eating severity, BMI, appetite, and gender, confirmed the robustness of our findings. For binge eating severity, the adjusted treatment effect was -1.10 (95% CI: -1.60 to -0.60, P < 0.001). For BMI, the adjusted treatment effect was -0.56 (95% CI: -1.02 to -0.10, P = 0.008). These results were consistent with the unadjusted analyses. Including gender in the model slightly reduced the treatment effect size (from η_p^2 = 0.295 to η_p^2 = 0.278) and the F-value (from 22.62 to 20.39), but the treatment effect remained robust and significant. Gender itself accounted for only 0.4% of unique variance, confirming that the treatment works equally well across genders. Side effects differed significantly between groups (Fisher's exact P = 0.039 at week 8 and P = 0.36 at week 12) (Table 4). No severe adverse events were reported.

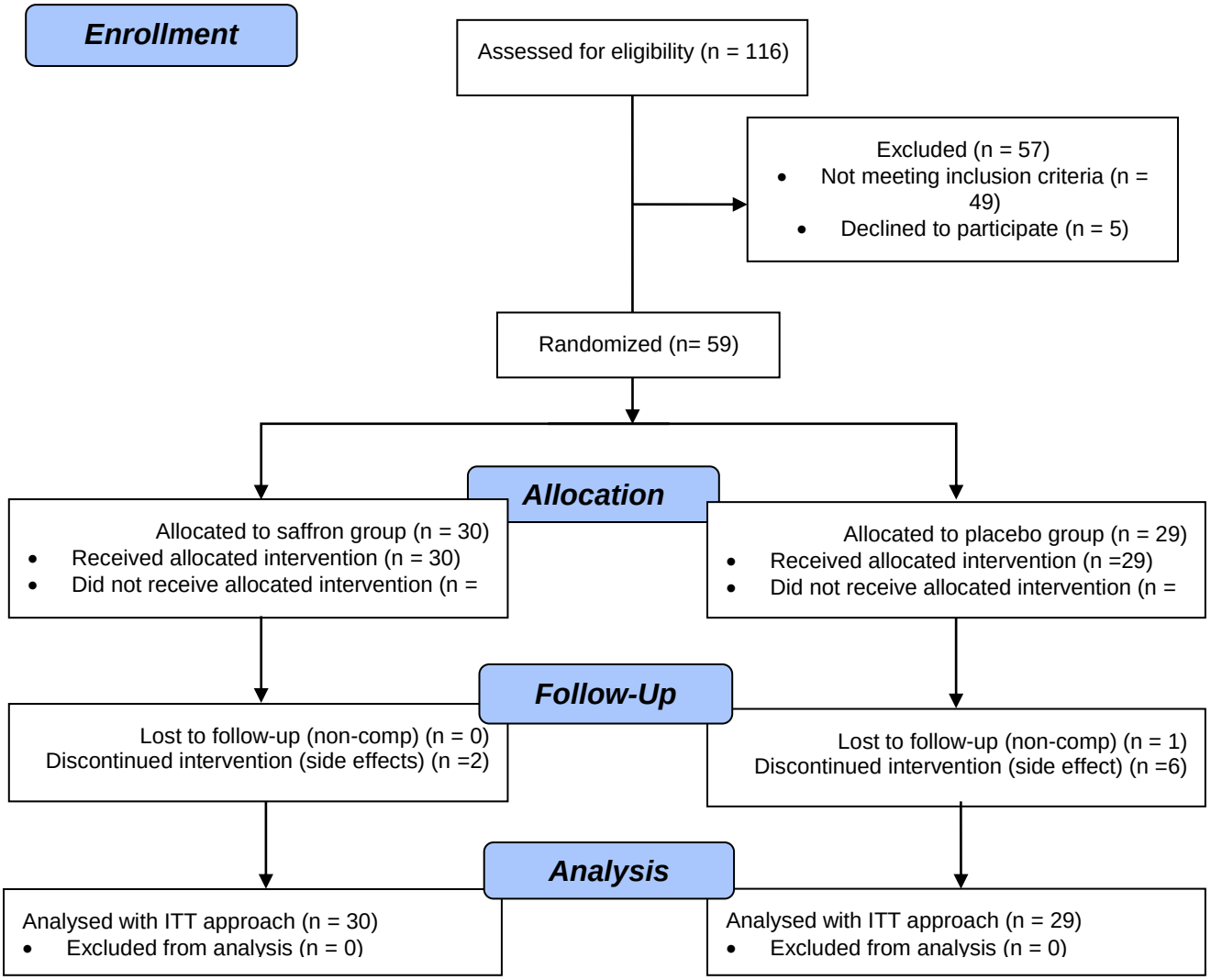

Figure 1. Flow Diagram of the Study of the Effects Saffron on Appetite and BMI of Subjects with binge Eating Disorder Compared with Placebo; ITT: Intention-to-Treat

Table 1. Baseline Characteristics of Study Participants in the Saffron Group compared with the Placebo Group

	Saffron(n = 30)	Placebo (n = 29)	P-value
Age	39 ± 6.94	38 ± 8.56	0.545
Gender			
Male	7 (23.3%)	11 (37.9%)	0.267
Female	23 (76.7%)	18 (62.1%)	
Marital status			
Single	11 (36.7%)	8 (27.6%)	
Married	17 (56%)	20 (69%)	0.637
Widowed/divorced	2 (6.6%)	1 (3.4%)	
Education			
Uneducated	4 (14%)	6 (20.7%)	
Educated	26 (86%)	23 (79.3%)	0.613
Smoking			
No	10 (33.3%)	17 (58.6%)	0.051
Yes	20 (66.7%)	12 (41.4%)	
Severity of binge eating			
Mild (1-3 episodes/week)	10 (33.3%)	6 (20.7%)	0.275
Moderate (4-7 episodes/week)	20 (66.7%)	23 (79.3%)	
Appetite (VAS)	17.33 ± 1.86	16.96 ± 1.76	0.440
BMI	30.51 ± 4.56	32.34 ± 4.83	0.139
Dietary calorie intake at baseline	2261 ± 578	2239 ± 526	0.855
Dietary carbohydrate intake at baseline	290 ± 69.89	296 ± 82.5	0.779
Dietary simple sugar intake at baseline	114.76 ± 40.62	103.04 ± 40.44	0.271
Dietary fat intake at baseline	81.86 ± 28.20	79.58 ± 23.6	0.73
Dietary protein intake at baseline	82.34 ± 26.18	83.97 ± 26.35	0.812

VAS: Visual Analogue Scale

Table 2. Changes in Study Outcomes and between-Group Mean Differences in the Saffron and Placebo Groups

		Saffron (mean ± SD)	Placebo (mean ± SD)	Between group mean difference ± Standard error of difference	p-value (Between group)	Cohen's D (95% CI)
Binge Eating Severity	Baseline	4.60 ± 1.54	4.51 ± 1.21	-1.16 ± 0.25	≤ 0.001*	-1.301 (-1.911 to -0.679)
	Endpoint	3.30 ± 1.44	4.34 ± 1.34			
	Change	-1.4 ± 1.06	- 0.23 ± 0.611			
	p-value [1] (Within group)	≤ 0.001	0.096			
Calorie intake	Baseline	2261 ± 578	2239 ± 526	-448 ± 113	≤ 0.001×	-1.03 (-1.581 to -0.483)
	Endpoint	1835 ± 491	2261 ± 573			
	Within group mean Change	-426 ± 571	+22 ± 219			
	p-value ‡ (Within group)	≤ 0.001	0.596			
Carbohydrate intake	Baseline	290.32 ± 69.88	295.94 ± 83.18	-32.06 ± 16.41	0.056×	-0.509 (-1.025 to 0.012)
	Endpoint	237.84 ± 58.06	275.53 ± 76.35			
	Change	-52.48 ± 72.66	-20.41 ± 51.18			
	p-value ‡ (Within group)	≤ 0.001	0.041			
Protein intake	Baseline	82.34 ± 26.10	83.97 ± 26.35	-9.19 ± 5.87	0.125×	-0.405 (-0.919 to 0.113)
	Endpoint	72.91 ± 29.18	83.74 ± 25.83			
	Change	-9.43 ± 26.04	-0.23 ± 18.61			
	p-value ‡ (Within group)	0.057	0.947			

		Saffron (mean ± SD)	Placebo (mean ± SD)	Between group mean difference ± Standard error of difference	p-value (Between group)	Cohen's D (95% CI)
Fat intake	Baseline	81.86 ± 28.20	79.58 ± 23.69	-21.45 ± 5.1	≤ 0.001×	-1.095 (-1.64 to -0.54)
	Endpoint	67.88 ± 26.46	87.06 ± 27.44			
	Change	-13.98 ± 22.26	7.47 ± 16.36			
	p-value ‡ (Within group)	0.002	0.020			
Sugar intake	Baseline	114.76 ± 40.62	103.04 ± 40.44	-24.09 ± 11.38	0.039 ×	-0.551 (-1.06 to -0.028)
	Endpoint	91.57 ± 39.77	104.78 ± 34.53			
	Change	-23.19 ± 52.2	1.74 ± 33.07			
	p-value‡ (Within group)	0.021	0.709			
BMI	Baseline	30.51 ± 4.56	32.34 ± 4.83	-0.61 ± 0.45	0.006 *	-0.428 (-0.936 to -0.085)
	Endpoint	29.93 ± 4.57	32.41 ± 4.28			
	Change	-0.62 ± 1.63	-0.09 ± 1.53			
	p-value⁞ (Within group)	0.008	0.498			
Appetite	Baseline	17.33 ± 1.86	16.96 ± 1.76	-3.34 ± 0.56	≤ 0.001×	-1.76 (-2.36 to -1.15)
	Endpoint	14.21 ± 2.38	17.17 ± 2.33			
	Change	-3.12 ± 2.04	-0.20 ± 1.71			
	p-value‡ (Within group)	≤ 0.001	0.695			

Footnote: Change scores represent the mean of individual-level paired changes (endpoint minus baseline). This value may deviate from the difference between group baseline and endpoint means, particularly when missing data are present, as it reflects within-participant changes rather than group-level means. Cohen's d was calculated as the between-group mean difference divided by the pooled standard deviation: $d = (M_1 - M_2) / SD\_pooled$, where $SD\_pooled = \sqrt{[(n_1-1)\ SD_1^2 + (n_2-1)\ SD_2^2] / (n_1+n_2-2)}$." After applying the Benjamini-Hochberg FDR correction, the following outcomes remained significant at q < 0.05: binge eating severity (q < 0.001), appetite (q < 0.001), calorie intake (q < 0.001), fat intake (q < 0.001), and BMI (q = 0.018)."

‡ P-value according to paired t-test

⁞P-value according to Wilcoxon signed ranked test

×P-value according to independent sample t-test

**P-value according to Mann-Whitney U-test*

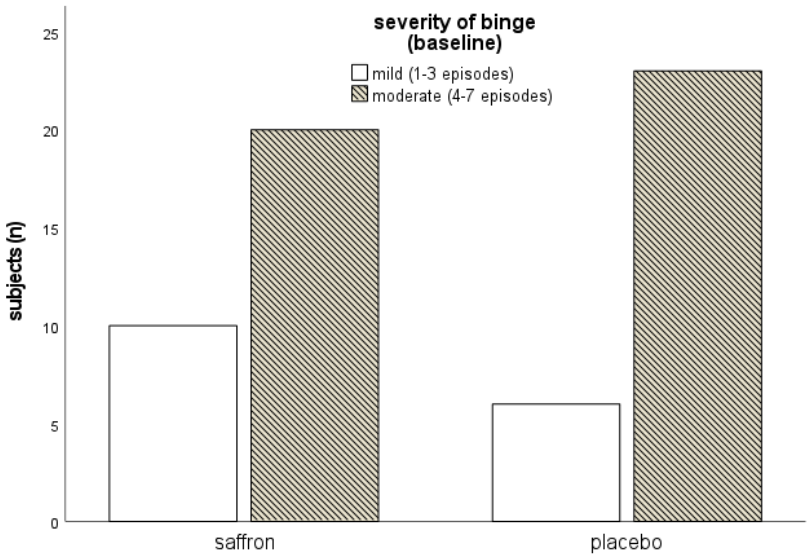

Figure 2. Binge Eating Severity (Number of Episodes) at Baseline and Comparison between Groups

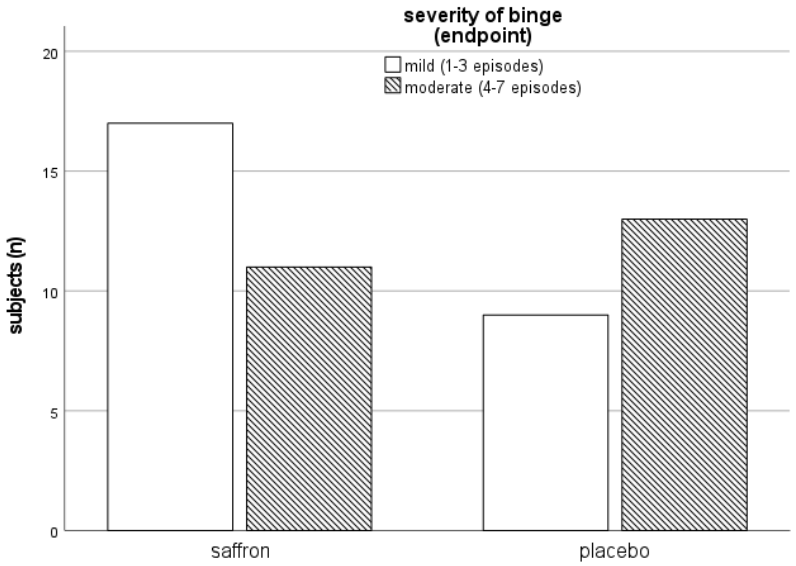

Figure 3. Binge Eating Severity (Number of Episodes) in each Group after 12 Weeks

Table 3. ANCOVA Table for Post-Treatment Binge Eating Severity after Controlling for Baseline Binge Eating Severity, Baseline BMI, Baseline Appetite, and Gender

Source	SS	df	MS	F	P
Treatment	15.664	1	15.664	22.615	< 0.001
Baseline Binge Severity	61.276	1	61.276	88.468	< 0.001
Baseline BMI	0.561	1	0.561	0.809	0.372
Baseline Appetite	0.184	1	0.184	0.265	0.609
Gender	0.140	1	0.140	0.199	0.657
Error	37.402	54	0.693		
Total	985.000	59			
Corrected Total	126.949	58			

SS: Sum of Square; MS: Mean Square, df: degree of freedom

Table 4. Frequency of Side Effects in Saffron and Placebo Groups at Weeks 8 and 12

Side effects	Week 8‡		Week 12 ¶	
	Saffron	Placebo	Saffron	Placebo
Headache	2 (6.7 %)	2 (6.9 %)	1 (3.3%)	1 (3.4%)
Reflux	2 (6.7 %)	0	0	0
Dyspepsia	2 (6.7 %)	0	0	0
Skin rash	2 (6.7 %)	0	0	0
Increased appetite	2 (6.7 %)	9 (31%)	2 (6.7 %)	9 (31%)
Menorrhagia	1 (3.3%)	0	1 (3.3%)	0
No side effect	19 (63.3%)	18 (62.1%)	26 (86.7%)	19 (65.5%)

‡, fisher's exact test P-value: 0.039 at week 8; ¶fisher's exact test P-value: 0.036 at week 12

Discussion

Saffron has been traditionally used in complementary medicine, but its active ingredients, crocin and safranal, have recently gained attention in evidence-based medicine (11, 14, 15). Previous studies have suggested using safranal in weight management due to its mood and appetite-regulating effects (16, 17). Antioxidant effects, blood sugar regulation, and neurotransmitter modulation have been proposed as its mechanisms of action (18, 19). The main finding of this trial was that 15

mg saffron capsules (twice daily) for 12 weeks can significantly improve binge eating behavior, appetite and weight-related factors. Participants who received saffron capsules showed a significant decrease in the number of binge-eating episodes and a slight but significant reduction in BMI compared with those in the placebo group.

The reduction of 1.16 binge episodes per week in the saffron group compared with the placebo group represents a moderate clinical improvement. Studies suggest that a reduction of ≥ 50% in binge eating episodes is considered a clinically meaningful response in BED trials (20). In our study, 40% of participants in the saffron group achieved this threshold, compared with 17% in the placebo group ($p = 0.056$).

This study is the first to examine saffron's impact on BMI in individuals with BED. The observed BMI reduction of 0.6 kg/m² over 12 weeks is modest. While statistically significant, it may not reach the 5-10% weight loss typically considered clinically meaningful for obesity management (21). These effects might be associated with decreased appetite and macronutrient intake, particularly a reduction in fat, carbohydrate and sugar intake. This research provides an innovative approach to understanding saffron's potential as an appetite suppressant. The findings are promising for individuals with BED who are engaged in medical treatment.

The enrolled subjects included patients with BED who were overweight at the time of selection (average BMI 30.51 ± 4.56 kg/m²). To clearly assess the effects of the saffron extract, participants agreed not to follow other diets or use other weight-loss products during the study. By only taking the supplement provided, we could reliably track changes in their appetite, weight (BMI), and binge eating frequency. In this study, the most remarkable outcome of saffron extract supplementation was a gradual decrease in the frequency of binging behaviors, demonstrated by a significant reduction in dietary calorie, fat and sugar intake, as well as both binge episodes and appetite following 12 weeks of treatment. Saffron helped reduce appetite and binge eating, which matched the increased feelings of fullness reported by participants, as measured by an appetite visual analogue scale and a three-day food intake record sheet.

Saffron Extract has been shown to have antioxidant and anti-inflammatory effects and to improve cognitive functions (11, 22). Studies have demonstrated that Crocus sativus extract might reduce anxiety and depression-like symptoms and significantly affect appetite (23). In the current clinical trial, the selected study population excluded those with other pathological eating disorders like bulimia nervosa and psychiatric diseases. The binge eating behavior could be triggered by mild anxiety or depressed mood, and previous studies have demonstrated that saffron extract may improve negative mood symptoms (24, 25). Esalatmanesh *et al.*, in their clinical trial, revealed that saffron is similar to fluvoxamine in the treatment of mild to moderate obsessive-compulsive disorder (26). This finding can support the proposed effect of saffron on compulsive eating. However, Akhondzadeh *et al.*, in a 12-week clinical study of the Crocus sativus extract (15 mg twice daily) on women with comorbid depression and overweight, revealed significantly decreased depression but not food craving (27).

Obesity and BED stem from mood and hormonal dysregulation. Appetite control involves both central and peripheral mechanisms (25). Despite the lack of evidence for direct peripheral mechanisms, saffron's appetite-suppressing effects could predominantly stem from the central nervous system and mood modulation (anxiolytic/antidepressant effects) (25, 28). While our findings demonstrate a causal association between saffron administration and improvements in binge eating, appetite, and BMI, we cannot definitively conclude that mood regulation mediated these effects (based on our method). The current study was not designed to test mediation. Future studies employing formal mediation analyses are needed to determine whether the effects of saffron on binge eating are driven primarily by mood modulation, appetite regulation, or independent mechanisms. Based on previous studies, saffron's antidepressant effects involve targeting key neurotransmitter systems, including dopaminergic and serotonergic pathways. These neurotransmitter systems are also involved in BED. Saffron's effects were comparable to those of synthetic drugs in small trials. However, the effective doses for comorbid obesity require further study (29, 30).

The safety of weight reduction medications and the effectiveness of herbal supplements for weight management are always controversial and vary significantly depending on their ingredients. While many popular formulas containing stimulants raise serious safety concerns and cause frequent adverse effects, preliminary research on saffron suggests it may be a better-tolerated and safer alternative (31, 32). In line with previous findings, we found that saffron intake was linked to very few or no adverse effects. The high tolerability allows us to confidently state that using saffron for three months appears safe.

However, we only tested saffron at a dose of 15mg twice a day (30 mg/day), and the dose-response relationship is still unknown. Investigating how different doses affect satiety and how safe they are, remain important topics for further studies. Although we did not test multiple doses, the dose we used was evidence-based, selected based on doses commonly used in previous literature that reported the effects of saffron extract on mood (31).

Limitation

In any clinical trial, the main implementation challenges are patient dropout and non-compliance with the study protocol. These were mitigated through multiple

telephone calls and reminders by the research team. Additionally, we used multiple imputation and ITT approaches to address these limitations. Moreover, administering only a single-dose capsule in this study limits our ability to draw dose-response conclusions. Furthermore, blinding success was not formally assessed, which we acknowledge as a limitation. However, no participant spontaneously reported identifying their group assignment.

Our study design does not permit causal mediation analysis. Therefore, the mechanism by which saffron reduces binge eating remains speculative and warrants further investigation using appropriate mediation analyses.

Conclusion

In conclusion, this 12-week randomized controlled trial (RCT) supports the hypothesis that saffron capsules (15 mg/twice daily) significantly reduce core symptoms of BED, including binge eating frequency, appetite, and dietary calorie intake. Furthermore, these capsules reduced fat and sugar intake in individuals with BED. As a result, saffron extract could contribute, although to a limited extent, to decreasing BMI and binge eating behaviors in individuals with BED. Hence, saffron extract could be a safe and useful supplement for medium-term use in people undergoing BED treatment.

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Conflict of Interest

The authors declare no conflict of interest related to this study.

Author's Contributions

Sasan Amiri: study concept, study performance, data gathering, approving the proof; Seyed-Ali Mostafavi: data analysis, writing the manuscript, and approving the proof; Ahmad Ali Noorbala1: study concept; Ariana Karkhaneh Yousefi: study performance; Shahin Akhondzadeh: study concept, study supervision, writing and approving the proof

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