Effects of Saffron Aqueous Extract and Its Main Constituent, Crocin, on Health-Related Quality of Life, Depression, and Sexual Desire in Coronary Artery Disease Patients: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial

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Abstract

Background: Depression and sexual problems are common in patients with coronary artery disease (CAD) and can influence their quality of life.

Objectives: The aim of this study was to compare the efficacy of saffron and its main constituent, crocin, in improving mental and sexual health and ultimately quality of life in CAD patients.

Methods: This double-blind, placebo-controlled, randomized clinical trial was carried out during 8 weeks in 3 groups, including 1 placebo and 2 intervention groups. The study sample included 58 CAD patients within the age range of 40 - 65 years, referred to Shahid Madani cardiovascular hospital, Tabriz, Iran, from April 2015 to November 2016. The intervention groups received saffron aqueous extract (SAE; 30 mg; n, 20) or crocin (30 mg; n, 19). All the groups completed the demographic questionnaire, Beck depression inventory-II (BDI-II), Hulbert index of sexual desire (HISD), and MacNew health-related quality of life questionnaire.

Results: The BDI-II score significantly decreased in the SAE (pre- and post test scores, 26.10 ±11.98 and 21.05 ±9.93, respectively) and crocin (pre- and post test scores, 27.89 ±8.46 and 22.68 ±8.01, respectively) groups (P < 0.001). After adjustments for age, sex, and diagnosis time, similar results were obtained. There was no significant difference between the crocin and SAE groups in terms of total BDI-II score at the end of the study (P = 0.999). SAE and crocin had no significant effects on HISD scores (P = 0.148 and 0.317, respectively). However, they could significantly improve the total quality of life and its subscales (P < 0.001).

Conclusions: SAE and crocin could improve depression and health-related quality of life in patients with CAD, whereas they had no significant effects on sexual desire.

Keywords: Saffron, Crocin, Depression, Quality of Life, Coronary Artery Disease

1. Background

Coronary artery disease (CAD) is one of the leading causes of disability and mortality worldwide (1). Many patients with CAD are exposed to a wide spectrum of mental and general health problems and experience impaired sexual function and functional difficulties, which can significantly influence their quality of life (QOL) (2-4). There is a dynamic negative interaction between different factors, which can lead to health problems in patients with cardiovascular problems (5).

Impaired sexual desire and activity can reduce QOL and increase the risk of depression and vice versa (6, 7). Recently, the ultimate goal of interventions in cardiovascular diseases has been not only to increase survival, but also to alleviate symptoms and improve physical, mental, and social functions (8). Assessment of health-related QOL, as an important health index, is valuable in patients with CAD, especially for evaluating the effects of interventions in clinical trials (8, 9).

Natural medicines, considering their fewer side effects and drug interactions in comparison with chemical drugs, are more acceptable among patients with chronic diseases (10). Saffron (Crocus sativus L.) is a traditional therapeutic agent (11), commonly used for the treatment of gastric,
mental, and cardiovascular disorders; moreover, it is used as an analgesic and antiinflammatory agent (12). Recent experimental and clinical findings indicate that saffron may have potentials in the treatment of mild to moderate depression, as well as some sexual problems (13-16). The main carotenoid in saffron, crocin, seems to be responsible for its beneficial effects on mental and sexual health (14, 17).

So far, no interventional studies have investigated and compared the possible effects of saffron and crocin on human mental and sexual health. Since high sexual and mental health is correlated with a higher QOL, the present double-blind, placebo-controlled, randomized intervention was designed to compare the efficacy of saffron and crocin in improving depression, sexual desire, and QOL in CAD patients.

2. Methods

2.1. Subjects

The subjects included males and females, aged 40 - 65 years with a confirmed diagnosis of CAD according to the angiographic findings. The subjects did not receive any psychotherapeutic or psychotropic drugs and only used common drugs for their cardiometabolic disorders. Hypertension was defined as systolic and/or diastolic blood pressure $\geq$ 150/90 mmHg or receiving antihypertensive medications (18).

The exclusion criteria were presence of autoimmune diseases, malignancies, insulin therapy, nursing profession, pregnancy, and hypersensitivity to saffron. Patients with heart attacks and those on antidepressants were also excluded from the study. The participants were recruited from Shahid Madani cardiovascular hospital in Tabriz, Iran. In the study design, we considered a power of 80% with a 2-sided $\alpha$ of 0.05 (type I error). The mean and standard deviation (SD) of differences on the female sexual function index (FSFI) were used, as reported in a study by Kashani et al. (15). The number of subjects was 20 per group. Considering an anticipated dropout rate of 10%, the sample size was measured at 23 subjects.

2.2. Preparation of SAE, Crocin, and Placebo Capsules

Saffron stigmas were purchased from Ghaenat farmlands in Khorasan, Iran. To prepare SAE, dried and milled stigmas were macerated in water for 72 hours. The mixture of plant and water was subsequently centrifuged for 5 minutes at 3000 rpm, and the supernatants were freeze-dried. Crocin was extracted and purified using our previously described method (19). Then, identical capsules with similar shapes, weights, and colors were filled with 30 mg of SAE/crocin and cornstarch (vehicle). The placebo capsules also contained the same vehicle.

2.3. Study Design

This study was designed as a double-blind, placebo-controlled, randomized clinical trial, conducted between April 2015 and November 2016. A total of 63 subjects met the inclusion criteria and were randomly assigned to the groups, using block randomization, which was generated by the random allocation software (RAS). The subjects randomly received capsules containing SAE (n, 21), crocin (n, 21), or placebo (n, 21) for 8 weeks. Overall, 58 (nearly 92%) patients remained in the study until the end. The clinical researchers, patients, and statistical analysts were all blind to the group assignments. This trial was registered at the Iranian registry of clinical trials (IRCT201512102017N26; www.irct.ir). All the participants signed a written informed consent form, and the ethics committee of Tabriz University of Medical Sciences approved the study.

2.4. Data Collection Tools

Health-related parameters were measured at baseline and after 8 weeks of intervention.

2.4.1. Beck Depression Inventory-II (BDI-II)

BDI-II is a self-report and widely applicable index for the assessment of depression severity. It evaluates 21 common symptoms of depression on a 4-point Likert scale, ranging from 0 (no distress) to 3 (maximum distress). The maximum BDI-II score is 63, which reflects the most severe symptoms. According to the cut-off scores, the patients were classified into minimal, mild, moderate, and severe depression groups (20). The Persian version of the questionnaire has been validated (21), and its internal reliability was found to be acceptable in the present study (Cronbach’s $\alpha$, 0.89).

2.4.2. Hulbert Index of Sexual Desire (HISD)

HISD consists of 25 questions rated on a Likert scale (0 - 4), with the total score ranging from 0 to 100. The maximum score represents the greatest sexual desire. The internal consistency of this questionnaire was determined in this study (Cronbach’s $\alpha$, 0.90). Moreover, its reliability and validity have been confirmed in Iran (22). In the present study, in the final section of the questionnaire, a general question on male sexual activity was added: “What is your common sexual problem?” “I have...” A) no problems, B) erection difficulties (frequency and duration), C) premature ejaculation, C) orgasm difficulties, D) sexual dissatisfaction, and E) others.
2.4.3. Health-Related QOL Questionnaire

The health-related QOL was evaluated using the MacNew instrument, designed exclusively to assess cardiac patients’ QOL (23). It consists of 27 questions in 3 subscales: emotional, physical, and social functioning. Each question has 7 options, ranging from “always” to “never”; higher scores indicate a better QOL (24). The internal consistency of this questionnaire was determined in the present study. Cronbach’s $\alpha$ for the MacNew domains was 0.94, 0.94, 0.93, and 0.96 for the emotional domain, social domain, physical domain, and total score, respectively. The Persian version of this instrument has been shown to be valid and reliable for group comparisons in clinical trials (25).

2.4.4. Statistical Analysis

Statistical analysis was performed using SPSS version 17.0 (SPSS Co., Chicago, IL, USA), based on the intention-to-treat (ITT) analysis. The normal distribution of variables was assessed and confirmed, using Kolmogorov-Smirnov and skewness-kurtosis tests. The quantitative variables are expressed as mean and SD, and categorical variables are expressed in number (percentage). The baseline characteristics were compared between the groups, using student t test, Chi square test, and Fisher’s exact test.

Analysis of variance (ANOVA) or Welch’s test was used to compare the baseline mean scores between the homogeneous and heterogeneous groups, according to the variances. In addition, paired t test was used for the comparison of mean differences within the groups (95% CI). Analysis of covariance (ANCOVA) was applied to compare the mean scores between the groups after the intervention. In
addition, Pearson’s correlation test was conducted to evaluate the relationship of changes in the QOL scores with changes in the BDI-II and HISD scores. P value < 0.05 was considered statistically significant.

3. Results

3.1. Participants

The participant disposition flowchart is presented in Figure 1. All the participants were sexually active, and no significant differences were observed in any of the baseline characteristics among the groups (Table 1).

3.2. Pre-to-Post-Intervention Changes in Depression, Sexual Desire, and Health-Related QOL

According to the BDI-II classification at baseline, 6 (10.3%), 7 (12.1%), 17 (29.3%), and 28 (48.3%) patients had minimal, mild, moderate, and severe depression, respectively. The percentage of changes in BDI-II scores at the end of the study in all the groups is presented in Figure 2. Clinical responses (reduction of baseline BDI-II score by 25% or more) were observed in 5 patients in the SAE group (25%), 3 patients in the crocin group (15.8%), and 1 patient in the placebo group (5.3%).

Paired t test comparisons revealed that both SAE and crocin interventions yielded significant improvements in the mean BDI-II scores compared to the baseline, while the scores remained unchanged in the placebo group (Table 3).

3.3. Between-Group Comparison of Changes in Depression, Sexual Desire, and Health-Related QOL

The mean baseline BDI-II and HISD scores were similar among the study groups. The ANCOVA analysis showed a significant difference between the groups in the mean BDI-II score after the intervention. After adjustments for age, sex, and diagnosis time, similar results were obtained (Table 2). According to the Sidak test, there were no significant differences between the crocin and SAE groups in the total BDI-II score at the end of the study (mean difference, 0.120; CI, -2.589 to 2.828; P = 0.999). The differences between the intervention (SAE and crocin) and placebo groups were significant (mean difference, -5.309; CI, -8.014 to -2.604; P < 0.001 and mean difference, -5.189; CI, -7.925 to -2.604; P < 0.001, respectively).

The between-group comparison of the mean HISD score did not show any significant differences at the end of the study; the differences remained insignificant after adjustments for age, sex, and diagnosis time (Table 2). There were no significant differences in the mean scores of QOL and its subscales between the study groups at baseline (Table 3). Except the social domain, the mean scores of other domains (emotional, physical, and total) were significantly different among the groups at the end of the study. After adjustments for age, sex, and diagnosis time, the mean scores of physical and social domains were not significantly different among the groups (Table 3).

According to the Sidak test, the mean differences in the total QOL scores between the intervention (SAE and crocin) and placebo groups were 0.382 (CI, 0.164 to 0.600; P < 0.001) and 0.244 (CI, 0.023 to 0.466; P = 0.026), respectively. The pairwise comparison showed significant differences between the groups in the mean score of emotional domain; the mean difference was 0.209 (CI, 0.015 to 0.403; P = 0.030) between the SAE and crocin groups, 0.552 (CI, 0.357 to 0.746; P < 0.001) between the SAE and placebo groups, and 0.342 (CI, 0.145 to 0.539; P < 0.001) between the crocin and placebo groups. In the physical domain, there was a significant difference in the mean score only between the SAE and placebo groups before adjustments (mean difference, 0.290; CI, 0.005 to 0.574; P = 0.045).

3.4. Correlation Assay

The correlation of differences in the mean BDI-II scores and the mean scores of total QOL and its subscales was analyzed, and a relatively strong negative relationship was observed (P < 0.001; total score: R, -0.694; emotional score: R, -0.597; physical score: R, -0.583; and social score: R, -0.538).
### Table 1. The Demographic and Baseline Clinical Characteristics of the Samples (N, 58)

| Variables                  | SAE (n, 20)       | Crocin (n, 19)    | Placebo (n, 19)   | P value<sup>b</sup> |
|----------------------------|-------------------|-------------------|-------------------|---------------------|
| Age, years                 | 53.70 ± 6.23      | 56.16 ± 7.22      | 56.63 ± 6.08      | 0.326               |
| Sex, male                  | 11 (55)           | 10 (52.6)         | 8 (42.1)          | 0.800               |
| Family history of CAD      | 10 (50.0)         | 8 (42.1)          | 7 (36.8)          | 0.755               |
| Smoking                    |                   |                   |                   |                     |
| Current                    | 1 (50.0)          | 4 (21.1)          | 3 (15.8)          | 0.331               |
| Past                       | 5 (25.0)          | 3 (5.8)           | 0 (0.0)           |                     |
| Hypertension               | 9 (45.0)          | 14 (73.7)         | 12 (63.2)         | 0.194               |
| Diabetes mellitus          | 2 (10.0)          | 4 (21.1)          | 3 (15.8)          | 0.607               |
| Physical activity          |                   |                   |                   | 0.300               |
| Low                        | 0 (0.0)           | 1 (5.3)           | 2 (10.5)          |                     |
| Moderate                   | 18 (90.0)         | 17 (99.5)         | 13 (82.8)         |                     |
| High                       | 2 (10.0)          | 1 (5.3)           | 4 (21.1)          |                     |
| Body weight, kg            | 82.90 ± 11.72     | 81.74 ± 13.57     | 76.37 ± 11.27     | 0.218               |
| BMI, kg/m<sup>2</sup>      | 28.55 ± 2.17      | 28.27 ± 4.01      | 27.78 ± 3.04      | 0.745               |
| Systolic blood pressure, mmHg | 123.3 ± 7.90    | 122.3 ± 7.90      | 120.4 ± 7.90      | 0.65                |
| Diastolic blood pressure, mmHg | 74.9 ± 9.23    | 75.1 ± 8.70       | 77.2 ± 10.52      | 0.34                |

Abbreviations: CAD, Coronary Artery Disease; SAE, Saffron Aqueous Extract.

<sup>a</sup> Numerical variables are expressed as mean ± SD and categorical variables are expressed as number (%).

<sup>b</sup> P value for between-group comparisons with student t test, Pearson’s Chi square test, and Fisher’s exact test.

### Table 2. The Effects of Groups on the BDI-II and HISD Scores

| Variables                  | SAE (N, 20)       | Crocin (N, 19)    | Placebo (N, 19)   | P Value | P Value<sup>b</sup> |
|----------------------------|-------------------|-------------------|-------------------|---------|---------------------|
| BDI-II                     |                   |                   |                   |         |                     |
| Before<sup>b</sup>         | 26.10 ± 11.98     | 27.89 ± 8.46      | 27.42 ± 9.40      | 0.847   |                     |
| After<sup>c</sup>          | 21.05 ± 9.93      | 22.68 ± 8.01      | 27.47 ± 9.40      | < 0.001 | < 0.001             |
| Within-group MD<sup>d</sup> (95% CI) | -5.05 (-6.86 to -3.24) | -5.21 (-6.88 to -3.54) | 0.05 (1.80 to 9.91) |         |                     |
| P value                    | < 0.001           | < 0.001           | 0.953             |         |                     |
| HISD                       |                   |                   |                   |         |                     |
| Before<sup>b</sup>         | 40.05 ± 17.89     | 36.32 ± 13.39     | 28.79 ± 12.83     | 0.065   |                     |
| After<sup>c</sup>          | 42.10 ± 17.55     | 37.75 ± 15.96     | 30.84 ± 13.98     | 0.940   | 0.842               |
| Within-group MD<sup>d</sup> (95% CI) | 2.05 (-0.90 to 4.90) | 1.43 (-1.49 to 4.35) | 2.05 (-0.95 to 5.06) |         |                     |
| P value                    | 0.148             | 0.317             | 0.169             |         |                     |

Abbreviations: BDI-II, Beck Depression Inventory-II; CI, Confidence Interval; HISD, Hulbert Index of Sexual Desire; MD, Mean Difference; SAE, Saffron Aqueous Extract.

<sup>a</sup> P value based on ANCOVA, adjusted for age, sex, and diagnosis time.

<sup>b</sup> Data are presented as mean ± SD. Statistical analyses are performed by means of one-way ANOVA.

<sup>c</sup> Data are presented as mean ± SD. Statistical analyses are performed by means of ANCOVA.

<sup>d</sup> Within-group mean difference (95% CI) based on paired t-test.

### 4. Discussion

According to the results of this trial, SAE and crocin could improve depression and health-related QOL in patients with CAD, while they had no significant influence on sexual desire. Several studies have indicated that CAD patients are generally prone to depression (26, 27). In line with previous studies, our findings showed that over 50% of patients had moderate to severe depression at baseline.
Table 3. The Effects of Groups on QOL and Its Subscales in the MacNew Instrument

| Variables                  | SAE (N, 20) | Crocin (N, 19) | Placebo (N, 19) | P Value | P Value* |
|----------------------------|-------------|----------------|-----------------|---------|---------|
| **Total QOL score**        |             |                |                 |         |         |
| Before^b                   | 4.00 ± 1.31 | 4.11 ± 0.98    | 3.72 ± 0.87     | 0.433   |         |
| After^c                    | 4.42 ± 1.18 | 4.39 ± 0.99    | 3.78 ± 0.97     | < 0.001 | 0.001   |
| Within-group MD^d (95% CI) | 0.42 (0.30 to 0.54) | 0.28 (0.19 to 0.37) | 0.05 (-0.12 to 0.22) |         |         |
| P value                    | < 0.001     | < 0.001        | 0.531           |         |         |
| **Emotional functioning**  |             |                |                 |         |         |
| Before^b                   | 3.75 ± 1.38 | 3.79 ± 0.98    | 3.65 ± 1.06     | 0.917   |         |
| After^c                    | 4.33 ± 1.13 | 4.16 ± 0.98    | 3.69 ± 1.04     | < 0.001 | < 0.001 |
| Within-group MD^d (95% CI) | 0.58 (0.40 to 0.76) | 0.37 (0.25 to 0.48) | 0.04 (-0.03 to 0.11) |         |         |
| P value                    | < 0.001     | < 0.001        | 0.249           |         |         |
| **Physical functioning**   |             |                |                 |         |         |
| Before^b                   | 4.07 ± 1.27 | 4.22 ± 1.05    | 3.68 ± 0.81     | 0.189   |         |
| After^c                    | 4.39 ± 1.18 | 4.45 ± 1.05    | 3.72 ± 0.97     | 0.046   | 0.065   |
| Within-group MD^d (95% CI) | 0.32 (0.19 to 0.44) | 0.22 (0.13 to 0.31) | 0.04 (-0.01 to 0.30) |         |         |
| P value                    | < 0.001     | < 0.001        | 0.722           |         |         |
| **Social functioning**     |             |                |                 |         |         |
| Before^b                   | 4.31 ± 1.52 | 4.48 ± 1.13    | 3.97 ± 0.98     | 0.350   |         |
| After^c                    | 4.61 ± 1.43 | 4.63 ± 1.14    | 4.06 ± 1.14     | 0.163   | 0.209   |
| Within-group MD^d (95% CI) | 0.30 (0.18 to 0.42) | 0.14 (-0.03 to 0.31) | 0.08 (-0.06 to 0.32) |         |         |
| P value                    | < 0.001     | 0.103          | 0.496           |         |         |

Abbreviations: CI, Confidence Interval; MD, Mean Difference; SAE, Saffron Aqueous Extract.

*P value based on ANCOVA, adjusted for age, sex, and diagnosis time.

Data are presented as mean ± SD. Statistical analyses are performed by means of Welch’s test.

Data are presented as mean ± SD. Statistical analyses are performed by means of ANCOVA.

Within-group mean difference (95% CI) based on paired t-test.

In this regard, a meta-analysis revealed that depression is a risk factor for mortality in these patients, and it is necessary to develop practical interventional strategies, apart from psychopharmacological treatments (28).

Consistent with the present study, findings of some clinical trials support the use of saffron for the treatment of depression (29, 30). However, there is a limited number of studies investigating the therapeutic effect of crocin on depression (17). In this regard, the safety of SAE and crocin (30 mg daily) in patients with schizophrenia was evaluated during 12 weeks (31). In this study, no significant differences were found between SAE and crocin treatments in terms of reduction in the BDI-II scores.

Crocin (digentiobiosyl ester of crocetin) is a watersoluble carotenoid and an active component of saffron (11). Moreover, it has shown a functional interaction with the serotonergic system (32). On the other hand, some neurotransmitters, such as dopamine and serotonin, are dramatically affected in depression. According to a study by Talaei et al., saffron and its active constituent, crocin, can influence the level of some neurotransmitters in the brain (17). Human monoamine oxidase (hMAO) enzymes are potential targets for the treatment of depression. The results of a recent study demonstrated that saffron components might inhibit MAO (33); therefore, SAE and crocin can be used for the management of mental disorders.

CAD deeply affects sexual function in both men and women (34, 35), while sex is the basis of intimate relationships. Reduced sexual activity and satisfaction, erection problems, and orgasmic problems have been described in these patients (36). The patients in the present study also reported similar difficulties (data not shown). Physical disabilities, marital tensions because of impaired sexual activity, and reduced social support due to chronic CAD can influence QOL and increase the risk of depression (6, 37, 38).

Saffron is traditionally known as an aphrodisiac agent. An experimental study on male rats revealed this characteristic for saffron and crocin (14). In this regard, a pilot
study was conducted on male erectile dysfunction, reporting the beneficial effects of saffron on male sexual function (39). These studies measured the effects of saffron and its components on sexual dysfunction (erection problems) (14, 39). Our findings, documented by similar scores on HIMSD within and between the groups, indicated that sexual desire was not affected by the same dose of saffron or crocin.

According to the general question related to sexual activity in this study, the number of men who reported sexual compliance (erection frequency and duration) reduced in both SAE and crocin groups (data not shown). However, such questions are not adequate to fully assess the sexual problems of CAD patients. To obtain accurate results in this area, more appropriate and valid tools are needed.

Compared to the placebo group, our findings showed a significant improvement in most QOL domains in the intervention groups. An increase was reported in the total QOL, as well as emotional, physical, and social domains, except for the social domain in the crocin group, which was insignificant. The effects of both SAE and crocin were nearly similar on this health outcome; nonetheless, with respect to emotional functioning, SAE was more effective in comparison with crocin.

The application of health-related QOL questionnaires as endpoints in clinical trials is increasing (3). The results of the present trial revealed that any improvement in mood and depression status could modify all aspects of QOL, which is consistent with our hypothesis in this study. The results of this study cannot firmly show that improvement in depression leads to a better QOL. Overall, improvement in the physical state (documented by the MacNew instrument) could improve the patients’ mood.

4.1. Strengths and Limitations

The present study is the first report about the comparison of saffron and crocin efficacy in ameliorating depression and increasing QOL in CAD patients. Nevertheless, this study had some limitations. Considering the limited sample size, subgroup analysis based on sex was impossible. In fact, sexual behavior and depression patterns vary among men and women. To obtain comprehensive results, it is recommended to conduct further research on both sexes using a large sample size. Moreover, to completely assess sexual life quality in patients, it is suggested to concurrently use several valid and reliable instruments.

4.2. Conclusion

The results of this study indicated the efficacy of saffron and its active constituent, crocin, in the improvement of depression and health-related QOL. Although these agents can be used as suitable adjunct agents in CAD patients, large-scale trials are justified.

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Footnotes

Conflicts of Interests: The authors declare no conflicts of interest.

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