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Effects of a Topical Saffron (*Crocus sativus* L) Gel on Erectile Dysfunction in Diabetics: A Randomized, Parallel-Group, Double-Blind, Placebo-Controlled Trial

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Abstract

Erectile dysfunction is a man's persistent or recurrent inability to achieve and maintain erection for a satisfactory sexual relationship. As diabetes is a major risk factor for erectile dysfunction, the prevalence of erectile dysfunction among diabetic men has been reported as 35% to 90%. This randomized, parallel-group, double-blind, placebo-controlled trial investigated the effects of a topical saffron (*Crocus sativus* L) gel on erectile dysfunction in diabetic men. Patients were randomly allocated to 2 equal groups (with 25 patients each). The intervention group was treated with topical saffron, and the control received a similar treatment with placebo. The 2 groups were assessed using the International Index of Erectile Function Questionnaire before the intervention and 1 month after the intervention. Compared to placebo, the prepared saffron gel could significantly improve erectile dysfunction in diabetic patients ($P < .001$). This preliminary evidence suggests that saffron can be considered as a treatment option for diabetic men with erectile dysfunction.

Keywords

saffron, Crocus Sativus L, erectile dysfunction, diabetes

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Erectile dysfunction is the most common sexual dysfunction among men. It is defined as a persistent or recurrent inability to maintain erection for a satisfactory sexual relationship.[1,2] Around half of 40- to 70-year-old men in the United States have been found to suffer from erectile dysfunction.[2] Moreover, the cost of diagnosis, treatment, and follow-up of the condition has increased from $185 million in 1994 to $330 million in 2000.[3] This dysfunction is known to affect not only physical, psychological, and social health of parents and their families but also their quality of life.[4]

The risk factors for erectile dysfunction include aging, hypertension, cardiovascular diseases, hyperlipidemia, enlarged prostate, increased body mass, sedation, smoking, depression, and some medicines.[2-4] Diabetes has also been proven as a major risk factor for erectile dysfunction.[3,5] Furthermore, erectile dysfunction and cardiovascular diseases have similar risk factors, and erectile dysfunction has been suggested as a sentinel for future risk of cardiovascular events.[3,4] Research has revealed neuropathy, microvascular and macrovascular disorders, and impaired smooth muscle contraction to be among the common causes of erectile dysfunction in diabetic patients.[3] Erectile dysfunction treatment depends on the underlying cause of the condition and involves lifestyle modification, changes in the administered medicines, psychotherapy, psychosexual therapy, hormone therapy, use of oral, intraluminal, and intracavernous medicines, prosthesis and

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vacuum, vascular surgery, and a combination of alternative medicine and the mentioned methods.[2-4]

Saffron (*Crocus sativus* L) has been widely used as a spice and medicine for more than 3000 years in Iranian culture and medicine. It has long been recognized as a sexual stimulant.[6] Recent scientific evidence about the benefits of saffron in the treatment of depression, epilepsy, cancer, ischemic heart disease, impaired learning and memory, hyperlipidemia, diabetes, and erectile dysfunction confirms the prominent beliefs of the traditional Iranian medicine.[7-12] Moreover, primary experimental studies have indicated the effectiveness of saffron in treating erectile dysfunction.[13-15] Thus, given the worldwide prevalence of diabetes (0.5% to 2.0%),[5] the 3-fold prevalence of erectile dysfunction in diabetic men,[3,16] and primary evidence suggesting the beneficial effects of saffron on erectile dysfunction,[13-15] the present study aimed to determine the effects of a topical saffron gel on erectile dysfunction in diabetic men.

Methods

Study Design

This randomized, parallel-group, double-blind, placebo-controlled clinical trial recruited diabetic men with erectile dysfunction. The study was conducted at the Traditional Medicine Clinic affiliated to Mashhad University of Medical Sciences (Mashhad, Iran) during March to October 2014.

On receiving approval from the Ethics Committee of Mashhad University of Medical Sciences (#921988; February 22, 2014), the present clinical trial was registered at the Iranian Registry of Clinical Trials (IRCT ID: 201404071769N1; June 14, 2014). All patients signed informed consent forms (approved by the university) prior to the commencement of the study.

Married men with erectile dysfunction who were referred to the mentioned center from the urology and diabetes clinics of Mashhad University of Medical Sciences were recruited if they were 40 years and older and had diabetes. The exclusion criteria were history of central neurological and psychological disorders, drug allergy, or patients' willingness to withdraw from the study.

Gel Preparation

The formula suggested in traditional Iranian medicine was carefully followed to prepare a starch-based gel containing 1% saffron. All stages of gel preparation were performed in the pharmaceutical laboratory of School of Pharmacy, Shahid Beheshti University of Medical Sciences (Tehran, Iran). Saffron was obtained from Gonabad (a city in Iran, 34.3528°N, 58.6836°E) during November to December 2014. A golden yellow food color (code: E122-E160-E104, and permission 50/14694 from Food and Drug Organization of the Ministry of Health, Iran) was used to prepare a starch-based gel as placebo. Both saffron gel and placebo were packaged in similar 28-g tubes.

Intervention

The participants were asked to complete the Farsi version of the 15-item International Index of Erectile Function Questionnaire before the intervention. Both groups were trained to rub a pea-sized amount of the gel on their penis half an hour before a sexual intercourse. One month later, all participants were reassessed using the same questionnaire.

Randomization

A computer-generated randomization table was used to randomly and equally assign the participants to either the intervention group or the control group, in a 1:1 ratio. The saffron and placebo tubes were similar in appearance and had been coded at the laboratory. Hence, the participants, researchers, and the person who provided the subjects with the tubes were unaware of the coding. Decoding was conducted only after the completion of sampling and statistical analyses.

Assessment

The International Index of Erectile Function Questionnaire is a valid, multidimensional, self-report instrument.[17] The Farsi version of the questionnaire, which has been validated in previous cross-cultural validation studies,[18,19] was administered to assess erectile dysfunction in the current research. The 5 dimensions of this 15-item questionnaire include the following dimensions: erectile function: 6 items, score range 1 to 30; sexual desire: 2 items, score range 2 to 10; orgasmic function: 2 items, score range 1 to 10; intercourse satisfaction: 3 items, score range 0 to 15; and overall satisfaction: 2 items, score range 2 to 10. Total scores of the International Index of Erectile Function Questionnaire thus range between 5 and 75.[17] The main measured outcome was improved erectile function (determined based on increases in total score of the International Index of Erectile Function Questionnaire).

Statistical Analysis

Basic characteristics of the participants were compared using independent-samples t test and χ^2 test. Mann–Whitney U test was applied to compare baseline data and differences in pretrial and posttrial scores of the International Index of Erectile Function Questionnaire (total and its dimensions) between the intervention and control groups. All tests were performed in SPSS for Windows 18.0 (SPSS Inc, Chicago, IL) at a significance level of $P < .05$.

Results

Of the 74 patients who were referred to the Traditional Medicine Clinic, 10 were not eligible and 14 were excluded. The remaining 50 patients were randomly assigned to the intervention (treated with topical saffron gel) and control (treated with placebo) groups (25 patients each). All 50 patients completed the trial without any side effects or complications.

Table 1 shows the participants' basic characteristics. The mean age of the participants was 58.7 years (SD = 8.25, range = 40-76). As seen in Table 1, the 2 groups had no significant differences in age or time elapsed since the diagnosis of diabetes, hypertension, or hyperlipidemia.

The intervention and control groups were similar in terms of total International Index of Erectile Function Questionnaire scores and its 5 dimensions at baseline (all P values >.05 using Mann–Whitney U tests). However, as Table 2 shows, there were significant differences between the 2 groups on the pretrial and posttrial difference scores of the International Index of Erectile Function Questionnaire and its dimensions. In other

Table 1. Baseline Demographic and Clinical Characteristics.

Variables	Intervention Group (n = 25)	Control Group (n = 25)	P Value
Age, years (mean ± SD)	58.96 ± 8.71	58.44 ± 7.92	.826[a]
Diabetes duration, years (mean ± SD)	9.56 ± 7.46	8.40 ± 4.91	.520[a]
Hypertension presence, n (%)	12 (48%)	9 (36%)	.391[b]
Hyperlipidemia presence, n (%)	13 (52%)	11 (44%)	.571[b]

[a]Independent-samples *t* test.
[b]Chi-square test.

Table 2. The Scores of the Intervention and Control Groups in International Index of Erectile Function Questionnaire and Its Dimensions.

Parameter	Intervention Group (n = 25), Mean ± SD	Control Group (n = 25), Mean ± SD	*P* Value[a]
IIEF-15 score			*P* < .001
Pretrial	34.52 ± 4.07	36.44 ± 3.66	
Posttrial	44.32 ± 3.90	37.56 ± 3.68	
Erectile function			*P* < .001
Pretrial	12.92 ± 1.81	13.56 ± 1.67	
Posttrial	17.64 ± 1.87	13.88 ± 1.67	
Sexual desire			*P* < .001
Pretrial	6.08 ± 0.45	6.20 ± 0.45	
Posttrial	6.96 ± 0.38	6.32 ± 0.44	
Orgasmic function			*P* < .001
Pretrial	4.60 ± 0.71	5.12 ± 0.72	
Posttrial	5.56 ± 0.65	5.12 ± 0.72	
Intercourse satisfaction			*P* < .001
Pretrial	5.72 ± 0.85	6.20 ± 0.77	
Posttrial	7.56 ± 0.77	6.40 ± 0.78	
Overall satisfaction			*P* < .001
Pretrial	5.20 ± 0.58	5.36 ± 0.50	
Posttrial	6.60 ± 0.56	5.84 ± 0.52	

Abbreviation: IIEF-15, International Index of Erectile Function Questionnaire.
[a]Mann–Whitney *U* tests on the pre- and posttrial difference scores.

words, the prepared saffron gel was significantly more effective than placebo on improving erectile function.

Discussion

The present study aimed to assess the efficacy of a topical saffron gel in the treatment of erectile dysfunction in diabetic men. Considering the significantly higher International Index of Erectile Function Questionnaire scores after the application of the prepared saffron gel (compared to the control group), treatment with saffron had a significant beneficial effect on erectile dysfunction in diabetics. Similar results were also obtained in all 5 dimensions of the questionnaire, that is, erectile function, sexual desire, orgasmic function, intercourse satisfaction, and overall satisfaction.

Despite a comprehensive search, the authors failed to find a previous study on the effectiveness of saffron on erectile dysfunction in diabetics. Meanwhile, several studies have suggested the positive effects of saffron on erectile dysfunction in nondiabetic patients. A study used International Index of Erectile Function Questionnaire and RigiScan to assess the efficacy of oral saffron (200 mg/day) in men with erectile dysfunction. It reported a significant improvement in erectile function of the patients after 10 days ($P < .001$).[14] A randomized controlled clinical trial sought to determine the efficacy and tolerability of saffron (30 mg twice a day) in married men with major depression and fluoxetine-related sexual dysfunction.[15] It finally recommended saffron as an effective and tolerable drug for the treatment of sexual dysfunction. In another study, a group of rats were injected with constituents of saffron (safranal and crocin) and their sexual behaviors were compared with those of a group receiving Sildenafil.[13] They found that while safranal had no significant effects, all doses of crocin increased the frequency of erection and sexual desire. In contrast to the aforementioned studies, a recent crossover trial on 346 patients with erectile dysfunction administered the International Index of Erectile Function Questionnaire reported the oral intake of saffron (30 mg twice daily) to have no particular effects on erectile function in men.[20] This inconsistency may be attributed to the quality and cultivation site of saffron, the applied dosage, and the formula of the prepared drug.

Despite long-standing attention to alternative treatments of erectile dysfunction, the mechanism of action and benefits of each treatment option should be well researched before its application.[3] The holistic perspective of Iranian medicine justifies the effect of saffron on erectile dysfunction by its ability to strengthen the heart and increase libido, warmth, and vasoconstriction.[9,11,12] Modern pharmacology attributes the effectiveness of saffron in the treatment of erectile dysfunction to its crocetin content. Crocetin is believed to enhance nitric oxide synthase activity in vascular endothelium and promote the production of nitric oxide (a major neurotransmitter involved in erection[1-3]).[8] These preliminary results emphasize the need for further research to clarify the mechanism through which saffron affects erectile dysfunction from the perspectives of both Iranian medicine and modern pharmacology. Since erectile dysfunction has a complex and varied pathogenesis in diabetics and one third of the patients require invasive treatments due to failure of first-line treatments (oral drugs) or drug interaction,[1,4] such research can lead to new methods for the treatment of erectile dysfunction.

Limitations

To the best of our knowledge, the present trial was the first to evaluate the effects of saffron on erectile dysfunction in diabetic men. However, we did not assess marital satisfaction among the participants' wives. Moreover, the participants' lifestyle was not investigated. Finally, this trial only focused on the effects of saffron on erectile dysfunction in diabetic men. Due

to these limitations, further research is required to increase the generalizability of our findings.

Conclusion

The current trial provided primary evidence suggesting the efficacy of topical saffron in the treatment of erectile dysfunction in diabetic men. Therefore, saffron can be considered a treatment option for these patients before the application of invasive treatments. Nevertheless, definitive conclusion on the efficacy of this traditional Iranian medicine in the treatment of erectile dysfunction requires further studies with more sophisticated designs.

Authors' Note

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Author Contributions

The protocol of this study was developed by HM, SMN, and HAE. Clinical assessment of the patients based on the inclusion and exclusion criteria was performed by AS, AAA, and HM. The saffron and placebo gels were prepared by MKN. HAE, HM, and AK were involved in data collection and analysis. Initial drafting of the article was carried out by HM and AK. The draft was revised by all authors. The final version was prepared by HM.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The study was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (#921988; February 22, 2014).

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