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Therapeutic effects of saffron (*Crocus sativus* L.) and its constituents on reproductive systems: A review

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Abstract
Saffron (*Crocus sativus* L) belongs to the family Iridaceae. The plant contains important constituents like crocetin, picrocrocin, safranal (main component for characteristic aroma). Safranal is the aglycon of picrocrocin; those are responsible for many pharmacological actions. In Unani and Ayurveda saffron is used to cure chronic diseases such as asthma, arthritis, skin diseases, spasmodic disorders, digestive disorders, kidney disorders. Saffron is also useful in liver and spleen enlargement. According to global statistics, the susceptibility to premature ejaculation is considered as a significant matter and can be important in health planning in any community. Several strategies for treatment and prevention of the sexual weakness have provided that the use of herbal remedies seems effective and useful. Considering the available findings, the present study aims to introduce saffron as a prophylactic and therapeutic agent against premature ejaculation disorders. Our literature review showed that C. sativus and its components can be considered as promising agents in the treatment of premature ejaculation disorders.

Keywords: Saffron, *Crocus sativus*, crocin, picrocrocin, reproductive disorders

Introduction
Saffron, *Crocus sativus* L., is a perennial spice species belongs to the family of Iridaceae and has been spread out in Mediterranean and west of Asia from 10 west to 80 east degrees of geographical longitude, as well as from 30 to 50 north degrees of geographical latitude and up to 1000 meters from sea level [1]. The name saffron is commonly used to refer both to the spice and the plant itself. Some archaeological and historical studies indicate that domestication of saffron dates back to 2,000-1,500 years BC [2]. Saffron is currently being cultivated more or less intensively in Iran, India, Greece, Spain, Italy, Turkey, France, Switzerland, Israel, Pakistan, Azerbaijan, China, Egypt, United Arab Emirates, Japan, Afghanistan, Iraq and recently Australia (Tasmania) [3]. The name 'saffron' is derived from Arabic zá-faran which means 'be yellow' [4]. Saffron leaves (with producing about 1.5 t dry matter each year) can provide forage for about 160000 heads of cattle. Saffron petal is one of the by-products of fields that the amount of this byproduct is more than 10000 t each year. Nowadays, the only usage of saffron petals is dye extraction, which is not flourished yet [5].

Scientific classification

Kingdom	:	Plantae
Division	:	Magnoliophyta
Class	:	Liliopsida
Order	:	Asparagales
Family	:	Iridaceae
Genus	:	Crocus
Species	:	C. sativus [6].

Fig 1: *Crocus sativus* L

Phytochemical analysis

Saffron contains more than 150 volatile and aroma-yielding compounds. It also has many nonvolatile active components, many of which are carotenoids, including zeaxanthin, lycopene, and various α- and β-carotenes [7]. Saffron has golden yellow-orange color is primarily the result of α-crocin. This crocin is trans-crocetin di-(β-D-gentiobiosyl) ester (systematic (IUPAC) name: 8, 8-diapo-8,8carotenoic acid). Its formula is $C_{44}H_{70}O_{28}$ [8].

Crocin with weak bases it is converted into crocetin ($C_{34}H_{46}O_9$), peculiar sugar not quite identical with dextrose, hence called crocose. The resultant α-crocin is a carotenoid pigment that may comprise more than 10% of dry saffron's mass [8-9]. A second element underlying saffron's aroma is 2-hydroxy-4,4, 6trimethyl-2,5-cyclohexadien-1-one, the scent of which has been described as "saffron, dried hay like". The flavouring property of saffron is due to the bitter glycoside picrocrocin chemically it is 4-(β- D- glucopyranosyloxy)- 2, 6, 6- trimethylcyclohex- 1- ene- 1- carboxaldehyde. (Chemical formula- $C_{16}H_{26}O_7$). Safranal is less bitter than picrocrocin and may comprise up to 70% of dry saffron's volatile fraction in some samples [10-11]. It gives saffron much of its distinctive aroma. When saffron is dried after its harvest, the heat, combined with enzymatic action, splits picrocrocin to yield D-glucose and a free safranal molecule [12]. Dry saffron is highly sensitive to fluctuating pH levels, and rapidly breaks down chemically in the presence of light and oxidizing agents.

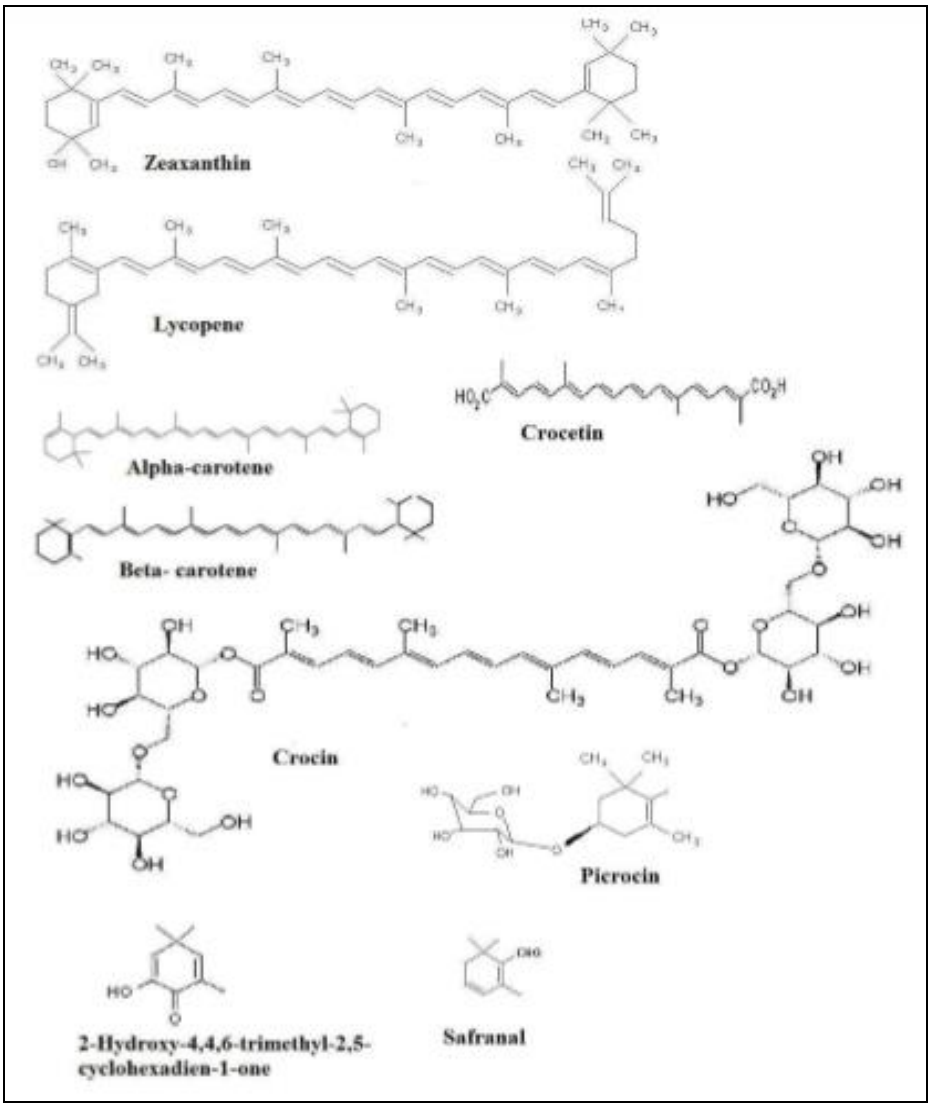

Fig 2: Chemical structure of *Crocus sativus*

Aphrodisiac activity

An aphrodisiac is a substance that stimulates the sexual activity or sexual desire in human/animals, either by psychophysiological or internal. The aqueous extract of saffron stigmas containing the compounds safranal and crocin was evaluated on male rats to check aphrodisiac activity. The result proved that the extract containing crocin had aphrodisiac properties [13].

Erectile dysfunction assigns a man's incapacity to retain an erection during sexual intercourse. Ali Shamsa *et al*. evaluated the effect of *Crocus sativus* L. on erectile dysfunction on male (human). The result confirmed that the saffron, only after taking it for ten days, it showed the beneficial effect in patients with huge number as well as duration of an erectile event [14].

Recently, different herbal remedies have been assessed as effective treatments for male infertility and other male sexual dysfunctions. Saffron has been known for centuries to have aphrodisiac properties. Moreover, the aphrodisiac activities of saffron aqueous extract and its constituent crocin, in male rats have been previously declared [15]. In a pilot clinical study on 20 men with erectile dysfunction, patients were observed for 10 days taking 200 mg tablets of saffron every morning. The results showed a statistically significant improvement in both tip and base rigidity and tumescence. Moreover, saffron was considered positively effective on sexual function of patients with erectile dysfunction even after a short time treatment [16]. However, this was a pilot study and the sample number was rather few. Additionally, there were no control group and no placebo was utilized. In a similar study to assess the efficacy and safety of saffron in erectile dysfunction, after 4 weeks of baseline evaluation, 346 men with erectile dysfunction received Sildenafil or saffron (30 mg BID) for 12 weeks. No significant improvements were observed in the international index of erectile function domains, Sexual Encounter Profile questions and Erectile Dysfunction Inventory of Treatment Satisfaction questionnaire scores with saffron administration. The authors reported that their findings did not support beneficial effects of saffron administration in men with erectile dysfunction [17]. This might be attributed to the low dose of saffron (30 mg BID) prescribed in comparison to the previous study. On the other hand, Safarinejad *et al* studied the effect of saffron vs. placebo on idiopathic male factor infertility on 260 infertile men with idiopathic oligo-asthenoteratozoospermia (OAT). Patients received either 60 mg/day saffron or placebo for 26 weeks. Afterwards, the two groups were compared with each other regarding changes in semen parameters and total seminal plasma antioxidant capacity. The results of the study showed saffron did not improve semen parameters in infertile men with idiopathic OAT [18]. In a case-report a 25-year-old woman with a two year primary infertility who was diagnosed with unilateral tubal blockage, received Unani herbal Majoon, one of its ingredients being C. sativus, for two successive cycles. The outcome was the patient's pregnancy two months after therapy. C. sativus L. was reported to recover infertility due to crocetin and flavonoids contents [19]. Earthiness, it cannot be directly concluded whether or not the positive result was due to saffron.

The aphrodisiac activities of C. sativus stigma aqueous extract and its constituents, safranal and crocin, were evaluated in male rats. The aqueous extract (80, 160, and 320 mg/kg body wt.), crocin (100, 200, and 400 mg/kg body wt.), safranal (0.1, 0.2, and 0.4 ml/kg), sildenafil (60 mg/kg body wt., as a positive control), and saline were administered intraperitoneally to male rats. Mounting frequency (MF), mount latency (ML), intromission latency (IL), and ejaculation latency (EL) were the factors evaluated during the sexual behavior study. Crocin, at all doses, and the extract, especially at doses 160 and 320 mg/kg body wt., increased MF, IF, and EF behaviors and reduced EL, IL, and ML parameters. Safranal did not show aphrodisiac effects. This study exhibited an aphrodisiac activity of saffron aqueous extract and its constituent crocin [20-21].

The aphrodisiac activities of *Crocus sativus* stigma aqueous extract and its constituents, safranal and crocin, were evaluated in male rats. The aqueous extract (80, 160 and 320 mg/kg bw), crocin (100, 200 and 400 mg/kg bw), safranal (0.1, 0.2 and 0.4 ml/kg), sildenafil (60 mg/kg bw, as a positive control) and saline were administered intraperitoneally to male rats. Mounting frequency (MF), intromission frequency (IF), erection frequency (EF), mount latency (ML), intromission latency (IL) and ejaculation latency (EL) were evaluated. Crocin, at all doses, and the extract, especially at doses 160 and 320mg/kg body wt., increased MF, IF and EF behaviors and reduced EL, IL and ML parameters. Safranal did not show aphrodisiac effects [22]. A randomized, parallel-group, double-blind, placebo-controlled trial was designed to investigate the effects of *Crocus sativus* gel on erectile dysfunction in diabetic men. Patients were randomly allocated to two equal groups (with 25 patients each). The intervention group was treated with topical saffron, and the control received a similar treatment with placebo. The two groups were assessed using the international index of erectile function questionnaire before the intervention and one month after the intervention. Compared to placebo, the prepared saffron gel significantly improved erectile dysfunction in diabetic patients (P <.001) [23]. The effects of different concentrations of saffron (*Crocus sativus*) aqueous extract (SAE), was evaluated in *in vitro* maturation (IVM) of immature mouse oocytes. Cumulus-oocyte complexes (COCs) were collected from 6-8 weeks old female mice ovaries. COCs were cultured in IVM medium supplemented with 0 (control), 5, 10, 20 and 40 µg/ml of (*Crocus sativus*) aqueous extract (SAE) in 5% CO_2 at 37℃. The rates of maturation, fertilization and development were recorded. The maturation rate was significantly higher in all groups treated with different concentrations of SAE compared with the control group ($p<0.05$). However, the lower concentrations of SAE (10 and 5 µg/ml in maturation medium) increased the fertilization rate of oocytes and *in vitro* developmental competence when compared with the control group ($p<0.05$). The authors conclude that addition of appropriate amounts of SAE to maturation medium improved oocyte maturation and embryo development [24]. The effects of different concentrations of saffron (*Crocus sativus*) aqueous extract (SAE) and its ingredient, crocin, were evaluated on the improvement of *in vitro* maturation (IVM) and subsequent *in vitro* fertilization (IVF) and embryo development of mouse oocytes. Cumulus oocyte complexes were collected from ovaries, and germinal vesicle oocytes were cultured in the presence of SAE and crocin. SAE was added at dosages of 5, 10, and 40 µg/m and crocin 50, 100, and 400 µg/ml. All dosages were added to maturation medium and a group without SAE or crocin was considered as the control group. Both SAE and crocin improved the rate of IVM, IVF, and *in vitro* culture. Addition of 40 µg/ml SAE to maturation medium significantly increased the rate of IVM, IVF, and *in vitro* culture ($p < 0.05$). Furthermore 100 µg/ml crocin significantly increased the IVM rate compared to the control

group ($p < 0.05$) [25]. A double-blind and placebo-controlled trial was designed to investigate the effect of saffron (stigma of *Crocus sativus*) on the symptoms of premenstrual syndrome. The study was carried out on women aged 20–45 years with regular menstrual cycles and experience of PMS symptoms for at least 6 months. Women were randomly assigned to receive capsule saffron 30 mg/day (15 mg twice a day; morning and evening) or capsule placebo (twice a day) for two menstrual cycles. The primary outcome measure was the daily symptom report, and secondary outcome measure was the Hamilton depression rating scale. The trial showed that saffron was effective in relieving symptoms of PMS. A significant difference was observed in efficacy of saffron in the total premenstrual daily symptoms and Hamilton depression rating scale [26].

Conclusions

Saffron and its constituents were shown to possess multiple useful effects on several diseases such as premature ejaculation disorders and antioxidant activity. Due to high safety level of this phytomedicine, it can be applied in clinical trials for majority of its effects. Some applications of saffron such as premature ejaculation disorders and antioxidant activities are sufficient for the subsequent phase of clinical trials or drug developments. However, most of others effects and applications of saffron require further clinical and animal studies.

References

1. Kafi MMH, Rashed A, Koocheki, Mollafilabi A. Saffron: Production Technology and Processing. Center of Excellence for Agronomy (Special Crops). Faculty of Agriculture, Ferdowsi University of Mashhad, Iran, 2002.
2. Grilli Caiola M. Saffron reproductive biology. Acta Hort. 2004; 650:25-37.
3. Nehvi FA, Wani SA, Dar MI, Makhdoomi BA, Allie, Mir ZA. New emerging trends on production technology of saffron, Proc. II nd IS on Saffron Bio. and Techno. Eds., A. Koocheki *et al*. Acta Hort. 2007; 739:375-381.
4. Winterhalter P, Straubinger M. Saffron-renewed interest in an ancient spice. Food Rev. Int. 2000; 16:39-59.
5. Eskandari-Torbaghan MR, Abbasi-Ali Kamar, Astarei Ali R. Effect of saffron (*Crocus sativus* L.) petals on germination and primary growth of cotton (*Gossypium hirsutum* L.). Acta Hort. 2007; 739:87-91.
6. Tarantilis PA, Tsoupras G, Polissiou M. Journal of Chromatography A. 1995; 699(1):107-18.
7. Phytochemical methods, A guide to modern techniques of plant analysis, J. B. Harborne, Third edition, 1998, 139.
8. Duke JA, Ayensu ES. Medicinal Plants of China Reference Publications, Inc. 1985 ISBN 0-917256-20-4.
9. Ben Frik, Wyk Michael wink, Medicinal plants of the world, 3rd edition, 2003, 116.
10. McGee H. On Food and Cooking: The Science and Lore of the Kitchen, Scribner, ISBN 0-684-80001-2, 2004.
11. Deo B. Growing Saffron – The World's Most Expensive Spice, Crop & Food Research (New Zealand Institute for Crop & Food Research), 2003, 20
12. Lust J. The Herb Book. Bantam books, ISBN 0-553-23827-2, 1983.
13. Hosseinzadeh H, Ziaee T, Sadeghi A. The effect of saffron, *Crocus sativus* L. stigma, extract and its constituents, safranal and crocin on sexual behaviors in normal male rats, Phytomedicine. 2008; 15:491-495.
14. Ali Shamsa, Hossein Hosseinzadeh, Mahmood Molaei, Mohammad Taghi Shakeri, Omid Rajabi. Evaluation of *Crocus sativus* L. (saffron) on male erectile dysfunction: A pilot study, Phytomedicine. 2009; 16:690-693.
15. Hosseinzadeh H, Ziaee T, Sadeghi A. The effect of saffron, *Crocus sativus* stigma, extract and its constituents, safranal and crocin on sexual behaviors in normal male rats. Phytomedicine. 2008; 15:491-495
16. Shamsa A, Hosseinzadeh H, Molaei M. Evaluation of *Crocus sativus* L. (saffron) on male erectile dysfunction: a pilot study. Phytomedicine. 2009; 16:690-693
17. Safarinejad MR, Shafiei N, Safarinejad S. An open label randomized, fixed-dose, crossover study comparing efficacy and safety of sildenafil citrate and saffron (*Crocus sativus* Linn.) for treating erectile dysfunction in men naive to treatment. Int J Impot Res. 2010; 22:240-250
18. Safarinejad MR, Shafiei N, Safarinejad S. A prospective double-blind randomized placebo-controlled study of the effect of saffron (*Crocus sativus* Linn.) on semen parameters and seminal plasma antioxidant capacity in infertile men with idiopathic oligoasthenoteratozoospermia. Phytother Res 2011; 25:508-516.
19. Sultana A, Rahman K, Nagaraj RB. Conception in unilateral right tubal blockage with herbomineral formulations: a case report. J Altern Complement Med. 2011; 17:557-561.
20. Rahimi M. Bull Env Pharmacol Life Sci. 2015; 4:69-81.
21. Hosseinzadeh H, Ziaee T, Sadeghi A. Phytomedicine. 2008; 15(6):491-5.
22. Hosseinzadeh H, Ziaee T, Sadeghi A. The effect of saffron, *Crocus sativus* stigma, extract and its constituents, safranal and crocin on sexual behaviors in normal male rats. Phytomedicine. 2008; 15(6, 7):491-495.
23. Mohammadzadeh-Moghadam H, Nazari SM, Shamsa A, Kamalinejad M, Esmaeeli H, Asadpour AA *et al*. Effects of a topical saffron (*Crocus sativus* L) gel on erectile dysfunction in diabetics: A randomized, parallel-group, double-blind, placebo-controlled trial. J Evid Based Complementary Altern Med, 2015, doi:10.1177/2156587215583756
24. Tavana S, Eimani H, Azarnia M, Shahverdi A, Eftekhari-Yazdi P. Effects of saffron (*Crocus sativus* L.) aqueous extract on *in vitro* maturation, fertilization and embryo development of mouse oocytes. Cell J. 2012; 13(4):259-264.
25. Mokhber Maleki E, Eimani H, Bigdeli MR, Ebrahimi B, Shahverdi AH, Golkar Narenji A *et al*. A comparative study of saffron aqueous extract and its active ingredient, crocin on the *in vitro* maturation, *in vitro* fertilization, and *in vitro* culture of mouse oocytes. Taiwan J Obstet Gynecol. 2014; 53(1):21-25.
26. Agha-Hosseini M, Kashani L, Aleyaseen A, Ghoreishi A, Rahmanpour H, Zarrinara AR *et al*. *Crocus sativus* L. (saffron) in the treatment of premenstrual syndrome: a double-blind, randomised and placebo-controlled trial. International Journal of Obstetrics and Gynaecology, 2008, dio:10.1111/j.1471-0528.2007.01652.x