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Review article

Therapeutic Application of Saffron for Improvement of Women's Health: A Review of Literature

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Abstract

Saffron or *crocus sativus* L. (C. sativus) has been widely used as a food additive as well as a therapeutic agent in traditional medicine for centuries, especially in Asian countries. This spice consists of three bioactive components, including picrocrocin, safranal, and crocin, which exert alleviating effects in a wide range of disorders (*e.g.*cardiovascular, respiratory, gastrointestinal, neurodegenerative, psychiatric and female-specific disorders). Anti-nociceptive, anti-inflammatory, and anti-oxidative characteristics were reported for this herbal agent. Additionally, several studies have addressed the potential role of saffron in modulating the serotonergic system, which could be helpful in treatment of some diseases specific to women such as Premenstrual Syndrome (PMS), Postpartum Depression (PPD), postmenopausal symptoms, and sexual dysfunction. Nowadays, use of herbal medicine instead of chemical prescriptions has become very popular due to their generally lesser side effects and cultural acceptability. In the present report, we provided an overview of the current literature regarding the potential effects of saffron on women's health. Taken together, saffron seems a spice with strong beneficial impacts on various aspects that a woman might challenge with. Further trials could pave the way for the introduction of saffron as a routine safe treatment of aforementioned conditions in women population.

Keywords: Female-specific disorders, Premenstrual syndrome, Postmenopausal symptoms, Postpartum depression, Saffron, Sexual dysfunction

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Introduction

Saffron is derived from the stigma of *lily-like Crocus sativus (C.sativus)*, a perennial stemless herb belonging to the Iridaceae family and has been used for therapeutic purposes for thousands of years (1). Saffron, known as "red gold", is widely cultivates in Iran, India, and Mediterranean countries; therefore, most researches on potential effects of this spice originate from these regions (2). The external feature of saffron is as follows: three stigmas are hung on the petals of the colored flower of saffron and each flower has three yellow stamens without any active compound. On the other hand, stigmata of *C. sativus* has three bioactive ingredients, including, crocin, safranal and picrocrocin, which are responsible for the color, aroma and bitter taste of saffron, respectively (3). Notably, extra compounds such as lycopene, B vitamins and zeaxanthin are also present in this herbal agent (4).

For centuries, saffron has been extensively used in folk medicine in Asian countries, especially in Persia, to treat a wide range of diseases from physical discomforts like spasm, pain, disturbed gastrointestinal function and respiratory problems to different mental abnormalities (*e.g.*depression) (5,6). Through recent decades, the evidence related to the saffron therapeutic characteristics has prominently evolved. Hence, there is growing interest into using the extractions of this herb for treatment of diseases (2).

Females account for a higher proportion of neuropsychiatric conditions during reproductive events, probably due to sensitivity to fluctuations in the concentrations of their hormones, particularly sex hormones (7,8). It has been shown that these mental disorders are associated with deficits in serotonergic pathways (9). Therefore, Selective Serotonin Reuptake Inhibitors (SSRI) are commonly prescribed in the attempt to attenuate the negative outcomes. The consumption of antidepressant agents like Selective Serotonin Reuptake Inhibitors (SSRI) is higher in females because of higher prevalence of mood disorders among this population; accordingly, they are more prone to experience adverse effects related to these medications (i.*e.*sexual dysfunction) (10). In this respect, there is ongoing efforts on discovering an intervention that could modulate the serotonergic system and restore quality of women's life. Several studies have claimed that saffron is able to increase serotonin levels within the nervous system by inhibiting the reuptake of serotonin at the synapse level (11,12). On another note, herbal medicine is considered as one of the main alternative options to conventional chemical treatments because of possibly better safety profile and cultural acceptability. Today, saffron has been proposed as an appropriate treatment for several female-specific ailments, including Premenstrual Syndrome (PMS) (13), Postpartum Depression (PPD) (14), postmenopausal symptoms (15) and sexual dysfunction (16). Thereby, in this report, we aimed to address how saffron could be employed to improve general health of women suffering from common female-specific diseases.

Main constituents and chemical properties

To explain the chemical properties of saffron, the three main bioactive metabolites of this spice should be discussed. Saffron contains picrocrocin, safranal and crocin which are responsible for the bitter taste, aroma and color of this agent, respectively. Picrocrocin ($C_6H_{26}O_7$) is a bitter-tased constituent, which could be found in the stigmata of saffron. Picrocrocin, which is essentially a glycoside, is cleaved to glucose and aglycon; subsequently, the aglycon is converted into volatile compounds recognized as safranal ($C_{10}H_{14}O$) (17,18). Kuhn and Winterstein showed that the fresh stigmata does not smell until the drying and storage stage of saffron as picrocrocin is resistant to demolition. Originally, safranal with its aromatic property is a cyclic terpenic aldehyde (19). The next component is crocin, which is a member of carotenoids and is soluble in water due to its high contents of glycosyl. Literally, it is a crocetin digentiobiose ester ($C_{20}H_{24}O_4$) from the extensive family of natural dyes, although their provitamin function is not considerable (20,21).

Saffron contains two of the B vitamins including riboflavin and thiamine. The concentration levels of thiamin and riboflavin are 0.7-4 *μg/g* and 56-138 *μg/g*, respectively; the later range accounts for the highest amount of riboflavin among all natural foods (22). Likewise, essential fatty acids such as linoleic and linolenic are available in the petroleum ether extraction from the saffron bulbs (23). Nevertheless, saffron has not entered the market the main sources

of vitamins and fatty acids since the plant is not cost-effective.

Pharmacological applications of saffron

There is widespread support for a quite large number of possible pharmacological uses of saffron. In folk medicine, saffron has been popular for its antispasmodic, sedative, expectorant, carminative, stimulant, diaphoretic, stomachic, eupeptic, anticatarrhal, aphrodisiac and emmenagogue effects (5). Additionally, a significant number of evidence-based animal studies and clinical trials have addressed the effectiveness and safety of saffron in improving numerous physical conditions. For instance, saffron has been recognized as a modulator of GI chemical functions that causes increased appetite as well as GI motility (24), a bronchodilator that is helpful for respiratory conditions like chronic bronchitis or coughing (25), a uterine sedative that could lead to relief from painful dysmenorrhea (26), a regulator of sexual function (16,27-29), a serotonergic regulator that ameliorates PMS symptoms (13,30), and a sedative for spasm and lumbar pains (31). Beyond that, saffron could exert beneficial effects on Central Nervous System (CNS) and therefore has been a candidate for treatment of mental disorders. In this term, one of the most general medicinal utilities of saffron is in treatment of mild to moderate depression where its efficacy is similar to approved drugs such as imipramine and fluoxetine (14,32-35). Moreover, it has been well-documented that saffron intake reduces the progression of neurodegenerative disorders such as Alzheimer's Disease (AD) (36).

Mechanisms of action

It has been well-established that two major bioactive ingredients of saffron, crocin and safranal, have remarkable anti-atherosclerosis, anti-diabetic, anti-oxidant, anti-platelet aggregations, anti-ischemic and hypolipidemic properties (37-39). Some advantages could be attributed to the ability of crocetin to increase the speed of oxygen transport and diffusivity into tissues (25,38). Besides, stigmata and petals of saffron have also shown anti-nociceptive and anti-inflammatory activities (40). The other mechanisms of action of saffron that majorly take place within the CNS are through modulation of neurotransmitter systems such as inhibiting reuptake of monoamine neurotransmitters (*i.e.*serotonin, dopamine, norepinephrine), antagonizing N-methyl-D-aspartate (NMDA) receptors, agonizing Gamma Aminobutyric Acid (GABA) receptors and facilitating Brain-Derived Neurotrophic Factor (BDNF) signaling. These activities justify the easing of depressive and premenstrual symptoms following saffron administration. Additionally, various mechanisms are proposed for saffron mechanism of action in treatment of AD, including protection against neurodegeneration and neurotoxicity; inhibition of β-amyloid aggregation; prevention of neurofibrillary tangle and senile plaques formation; suppression of the acetylcholinesterase activity and neuroinflammation reduction (36).

Safety and toxicity

Beyond the rooted application of saffron as a food additive, this spice has been used for therapeutic purposes in both traditional and evidence-based manners. Although saffron has appeared safe and well tolerable, its possible side effects should be investigated. A glimpse of literature indicates that mild toxicity with saffron could cause a number of complications, including but not limited to, dizziness, nausea, vomiting, and diarrhea; in addition to these side effects, numbness and distal paresthesia are probable in severe toxication (41). Taking a deeper look, hematological adverse events such as reduced platelet count might occur when saffron is prescribed at doses above 200 *mg/day* (42). Although the hematological complications of saffron was associated with elevation of coagulation time and inhibition of platelet aggregation in animal models (41), the results from two different clinical trials did not reflect such negative results (43,44). However, toxication with high doses of saffron and possible hematological side effects should not be underestimated, particularly during pregnancy period as it can lead to miscarriage (42,45,46).

There has been mounting clinical studies of the safe dose of saffron in different diseases like depression (32,33). For instance, two randomized clinical trials showed that 30 *mg/day* of saffron for 6 weeks exerts beneficial effects on depression associated with both postmenopausal and postpartum conditions while causing no serious adverse event (14,47). Moreover, preliminary studies on the safety of adjunctive saffron in the context of SSRI-induced sexual dysfunction provided information that taking 30 *mg/daily* of

saffron for 4 weeks attenuates sexual problems in a safe manner (16,48). Furthermore, Agha-Hosseini *et al* designed a randomized trial to investigate whether saffron could relieve symptoms of PMS and observed similar results in terms of safety (13).

In summary, the current evidence suggests that administration of saffron (30*mg/daily*) appears to be safe and efficacious in different female-specific diseases (*e.g.*postmenopausal and postpartum related depression, sexual dysfunction, PMS). On the other hand, excessive consumption of saffron has induced toxic effects and its lethal dose of 20 *g* has been reported (49,50). Consequently, saffron could be considered as a safe and non-toxic spice in therapeutic fields, although further long-term investigations are required to confirm this issue.

Premenstrual syndrome

PMS is characterized by a wide variety of recurrent emotional and physical symptoms and behavioral changes over the luteal phase of menstruation cycle, affecting 20-40% of women of reproductive age (51,52). Females affected by PMS always scuffle in negative effects on the social interpersonal and job-related aspects that lead to reduced quality of life. Several etiologies have been described for PMS; however, the multifactorial essence of these syndromes have given rise to incomplete insight into the exact pathogenesis of PMS (53). Abundant evidence hypothesizes that serotonergic dysregulation during the luteal phase play the most important role in the PMS presentations. This assumption was confirmed when women suffering from PMS experienced positive effects after taking serotonergic inhibitor agents (54,55). According to the evidence, saffron can play a therapeutic role in treatment of mild to moderate depression (32,33). Likewise, efficacy of saffron at the dose of 30 *mg/day* for 6 weeks was similar to imipramine, which is one of the most common medications in treatment of depression (56). Since the symptoms of depression and PMS overlap, Agha-Hosseini *et al* investigated whether receiving 15 mg capsules of saffron twice a day for two menstrual cycles could relieve PMS symptoms and found that saffron significantly improves the symptoms, presumably through serotonergic mechanisms (13). In another clinical trial, Rajabi *et al* assessed the efficacy of saffron on Pre Menstrual Dystrophic Disorder (PMDD), identified as the severe form of PMS, with the exactly same duration and dosage of saffron applied in trial of Agha-Hosseini *et al* Their results alongside those of previous studies support the evidence that saffron could be an efficacious agent in treatment of PMS and PMDD while causing few negligible complications (30).

Postpartum depression

PPD is a common complication after childbirth, which takes a huge toll on women and negatively affects offspring development. It has been reported that due to giving birth, 4-25% of women challenge with numerous consequences of PPD such as harm to mother-child relationship, which can adversely impact child cognitive, behavioral, emotional and physical perspectives (57, 58). Since the precise etiologies of mood balance and particularly depression are not fully understood, there are substantial barriers in developing the optimum treatment strategy for PPD. Howbeit, literature has addressed the serotonergic dysregulation as the main biological etiology of depressive symptoms (59). In this regard, most of the therapeutic interventions for PPD, including pharmacotherapy, psychotherapy and hormonal therapy were adopted from the conventional treatments used for Major Depressive Disorder (MDD). However, these therapies might not be ideal from the patients'perspective. As an example, breastfeeding women with PPD may refuse to take pharmacological treatments such as SSRI, which are the first-line therapies for moderate to severe PPD, due to their concern about the safety of their infant (15,60). As far as discussed previously, saffron has been considered as a part of folk medicine in Asia and particularly in Persia. Furthermore, there is lots of evidence revealing the potential characteristics of saffron as an alternative treatment for depression (61). Accordingly, a randomized clinical trial evaluated the efficacy and safety of saffron administration to breastfeeding mothers with minor PPD for eight weeks and the results were promising (15). Besides, another study was carried out to compare the efficacy and safety of saffron and fluoxetine in treatment of mild to moderate PPD. The results proposed saffron as effective as fluoxetine while it brought about fewer adverse effects than the classic anti-depressant (14). The saffron potential for turning into an alternative of current

medications used for PPD treatment can be justified by inhibitory effects of saffron components on reuptake of dopamine, norepinephrine and serotonin (40).

Postmenopausal symptoms

Menopause is a natural phase between the reproductive and non-reproductive phases that annually disturbs 25 million women's lives worldwide in various aspects (62). Menopause is often accompanied by physical complaints (*e.g.*vasomotor, vaginal and cardiovascular symptoms) and emotional changes (*e.g.*mood swing, depression, cognitive dysfunction) (63). Although Hormone Replacement Therapy (HRT) has been commonly used to relieve these problems, especially vasomotor symptoms, women usually seek out an alternative therapy because of serious complications that could occur following HRT such as increased risk of cardiovascular diseases, thromboembolic events, and some types of cancers (64,65). Regarding the therapeutic effects of saffron on depression, sexual dysfunction, as well as cardiovascular problems, a few studies examined the influences of this herbal agent on women at postmenopausal stage (66). Taavon*i et al* demonstrated that aphrodit, a herbal supplement containing a number of plants such as saffron, attenuates the menopausal symptoms (67). Another study showed that a mixture of 1000 *mg* chamomile, 120 *mg* fennel, and 60 *mg* saffron over 12 weeks could significantly improve physical and psychological domains in women population with postmenopausal symptoms (66). Further evaluation of the healing properties of saffron in postmenopausal phase has revealed that this agent could also be employed as an appropriate treatment for depressive symptoms and hot-flashes with no serious side effect (47). Succinctly, due to the absence of serious negative effects and the aforementioned positive therapeutic impacts, saffron as a traditional herbal spice might be a suitable alternative for the postmenopausal condition.

Sexual dysfunction

Sexual dysfunction as a globally common health problem is characterized by disturbances in desire, excitement, orgasm, as well as dyspareunia. It is estimated that 25-63% of women suffer from sexual dysfunction, which indicates that this problem is more common in women than men with a prevalence of 10-52% (68,69). The higher prevalence in women stems from several reasons such as physiological differences in genetical and anatomical structures between men and women. Furthermore, as women are more prone to depression, they are more likely to use antidepressant medications like SSRI and consequently experience its common sexual side effects (70). Several medications (*e.g.*sildenafil, buspirone, bupropion) have been used to decline the sexual adverse effects of SSRI (71-73); nevertheless, their response rates are variable and significant adverse events are probable (74). In this regard, there has been increasing interest into using herbal supplements like saffron that are well-known for their anti-depressive characteristics. As an example, Hosseinzadeh *et al* executed an animal experiment to assess the effects of saffron active metabolites on sexual behaviors. The results revealed sexual enhancement in rats following receiving saffron supplement, albeit their study was limited to the male gender (27). In a randomized placebo-controlled setting, the researchers administered saffron to women of reproductive age who had sexual dysfunction and reported alle*via*ting effects for this golden spice (75). Finally, we appraised the aphrodisiac effects of saffron on SSRI-induced sexual dysfunction. This clinical trial showed that saffron can safely and effectively improve some of SSRI-induced sexual problems such as lubrication, arousal, and pain, suggesting this herb as an appropriate adjunct when SSRI prescription seems necessary (16). Taken together, saffron could be considered as a safe herbal agent for increasing women's sexual performance.

Conclusion

Saffron exhibits beneficial effects in management of several female-specific disorders, as reflected in table 1. Given the conclusive scientific findings, therapeutic effects of this herbal agent and its active constituents on female-specific disorders are mainly due to their interaction with serotonergic system. According to the experimental and clinical studies, as saffron have few negligible side effects and is generally well tolerated, it could be considered as an alternative treatment for female-specific conditions such as PMS,PPD, postmenopausal symptoms and

Table 1. Randomized clinical trials of saffron effect on female-specific disorders

Population	Sample size	Type of administration compounds	Compared with	Duration	Results	Author (year) (reference)
Females aged 20-45 with regular menstrual cycle and PMS symptoms	50	Capsule of C. Sativus 15 *mg* bid	Placebo bid	2 menstrual cycles	A significantly better outcome than placebo	Agha-Hosseini (2008) (76)
Females aged 20-45 with PMDD	120	Capsule of C. Sativus 15 *mg* bid	Capsule of fluoxetine 20 *mg* bid Placebo bid	2 menstrual cycles	No significant difference in relieving symptoms A significantly better outcome than placebo	Rajabi (2020) (77)
New mothers aged ≥ 18 with mild-to-moderate PPD	60	Capsule of C. Sativus 15 *mg* bid	Placebo bid	8 weeks	A significantly better outcome than placebo	Tabeshpour (2017) (78)
New mothers aged 18-45 with mild-to-moderate PPD	68	Capsule of C. Sativus 15 *mg* bid	Capsule of fluoxetine 20 *mg* bid	6 weeks	Effective similar to fluoxetine	Kashani (2017) (79)
Females over 40 years of age with postmenopausal hot flashes	60	Capsule of C. Sativus 15 *mg* bid	Placebo bid	6 weeks	A significantly better outcome than placebo	Kashani (2018) (80)
Females aged 18-45 with fluoxetine- induced sexual dysfunction	38	Capsule of C. Sativus 15 *mg* bid	Placebo bid	4 weeks	A significantly better outcome than placebo	Kashani 2013 (81)

Bid: two times a day, PMS: premenstrual syndrome, PMDD: premenstrual dystrophic disorders, PPD: postpartum depression,

sexual dysfunction. However, further studies are warranted on the mechanism of action of saffron components in the context of these disorders.

Conflict of Interest

The authors have no conflict of interest to declare.

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