Biological effects and pharmacological activities of saffron of *Crocus sativus*

Iliass LAHMASS[1]*, Mouad EL KHOUDRI[2], Sabir OUAHHOUD[1], Mouad LAHMASS, Amine KHOULATI[1], Said BENYOUSSEF[3], Samira MAMRI[1], Mouhssine MEZIANE[1], Ennouamane SAALAOUI[1]

[1] *Laboratory of Biochemistry and Biotechnology, University Mohamed Ist , Oujda, Morocco*
[2] *Research Team: Materials, Environment and Sustainable Development (MEDD), Faculty of Sciences and Techniques of Tangier, BP 416 – Tangier, Morocco*
[3] *Research team: Biology, Environment and Health, Faculty of Science and Technology Errachidia, University of Moulay Ismaïl Meknes, Morocco*

Abstract: The medicinal uses of saffron (*Crocus sativus* Linnaeus) have a long history beginning in Asian countries since the Late Bronze Age. Recent studies have validated its potential to lower the risk of several diseases. Saffron has been suggested to be effective in the treatment of a wide range of disorders including coronary artery diseases, hypertension, stomach disorders, dysmenorrhea and learning and memory impairments. In addition, different studies have indicated that saffron has anti-inflammatory, anti-atherosclerotic, antidiabetic, antigenotoxic and cytotoxic activities. The anticonvulsant and anti-Alzheimer properties of saffron extract were shown in human and animal studies. The efficacy of *Crocus sativus* in the treatment of mild to moderate depression was also reported in clinical trial. Many of these medicinal properties of saffron can be attributed to a number of its compounds such as crocetin, crocins and other substances having strong antioxidant and radical scavenger properties against a variety of radical oxygen species and pro-inflammatory cytokines.

Keywords: *Crocus sativus*, pharmacology, crocin, safranal, antioxidant, saffron

1 Introduction

Since immemorial times, herbal plants have been used in virtually every culture throughout the world as a source of folk medicine (Schultes, 1978). Saffron is known today as the red gold of the world's spices; it corresponds to the stigma of the "*Crocus sativus* L. " which is a plant of the family of iridaceae (Moshe, 1999).

*Corresponding author. Tel.: +212629530036. E-mail address: iliass.lahmass@gmail.com

Crocus sativus can withstand very severe climatic conditions due to its morphology and physiology; that said, the saffron bulb is very fragile, fearing very clay soils. For saffron to grow, its cultivation must be at varying altitude above 650m and the soils must be well draining with high levels of clay; therefore, very light soils are not suitable for cultivation (Deo, 2003, Crozet et al., 2012).

The importance of this species is due to the origin of the properties of its dry stigmas, such as: gold yellow color, bitter flavor and fascinating aroma; these three characteristics are attributed, respectively, to three essential chemical molecules: crocin, picrocrocin and safranal (Melnyk et al., 2010).

Since antiquity this spice has been valued for several uses: at the traditional level, it is in various fields such as: gastronomy, used as a food dye, its power to change the flavor of food, as well as its fascinating aroma, cosmetics, painting, dyeing of textiles, in perfumery, and in certain religious rituals (Barkeshli and Ataie, 2002, Cardon, 2003, Mousavi and Bathaie, 2011), Saffron also, is recognized for having numerous and important biological properties among which are found sedative, antispasmodic, and stomachal stimulant activities (Sampathu et al., 1984) as well as antitumor (Abdullaev and Espinosa-Aguirre, 2004, Nair et al., 1995, Salomi et al., 1991). In Ayurveda, saffron is used to cure chronic diseases such as asthma and arthritis. It is also useful in treating cold and coughs. Ayurvedic medicines containing saffron are used to treat acne and several skin diseases. A paste of the spice can be used as a dressing for bruises and superficial sores.

Saffron also has various effects: hypolipidemic (Lahmass et al., 2018), anticonvulsant (Khosravan, 2002), anti-oxidant (Lahmass et al., 2017a, Karimi et al., 2010), anti-depressant (Hosseinzadeh and Nassiri-Asl, 2013) and anti-diabetic (Lahmass et al., 2017b, Elgazar et al., 2013).

2 Materials and methods

Information of this review article was collected by searching for the key-words "*Crocus sativus*", "saffron", "nervous system", "antioxidant effect", "clinical application", "animal studies", "in vitro and in vivo assay", "antibacterial activity", "antifungal effect", "crocin", "crocetin" and "safranal" in databases namely ISI Web of Knowledge, Medline/ Pubmed,

Science direct, Scopus, Google Scholar, Embase, Biological Abstracts and Chemical Abstracts.

3 Chemical compositions of saffron

The economic value of the *Crocus sativus* plant in world trade is reduced in its spice, known as saffron or stigma. It is also their biological and medicinal properties that have made it widely used in traditional, modern medicine and in several fields of industry.

The stigmas of the saffron flower contain many chemical substances. Carbohydrates, minerals, musilage, Vitamins (especially riboflavin and thiamine) and pigments including crocin, anthocianin, carotene, lycopene, zeaxantin, flavonoids, amino acids, proteins, starch, gums, and other chemical compounds have also been described in saffron (Abdullaev and Espinosa-Aguirre, 2004, Rios et al., 1996).

The saffron stigma, which is what basically forms commercial saffron, has a distinct and unique color, flavor and aroma and some of the groups of chemical compounds responsible for each of these properties have now been identified. One of its principal coloring pigments is crocin, belongs to a group of natural carotenoid commercially obtained from the dried stigma of *Crocus sativus*. It has a deep red color, forms crystals with a melting point of 186 °C and is easily soluble in water. In addition to crocin, saffron contains crocetin as a free agent and small amounts of the pigment anthocianin, a-carotene, b-carotene, and zeaxantin (Melnyk et al., 2010).

The principal element giving saffron its special ‘‘bitter’’ flavor is the glycoside picrocrocin. This bitter tasting substance can be crystallized and produces glucose and the aldehyde safranal by hydrolysis (Tarantilis and Polissiou, 1997).

The main aroma factor in saffron is safranal, which biological activities of saffron comprises of about 60% of the volatile components of saffron. In fresh saffron, this substance exists as a stable picrocrocin but as a result of heat and with the passage of time, it decomposes releasing the volatile aldehyde, safranal (Carmona et al., 2005, Lage and Cantrell, 2009).

Saffron bioactive compounds, namely crocins, picrocrocin and safranal provide, respectively, color, taste and aroma characterizing this spice. All crocins are crocetin esters, in which glucose and gentiobiose occur as carbohydrate residues (Table 1, Figure 1) (Bouvier et al., 2003).

Table 1: Chemical structures of major crocetin esters present in saffron

Denomination	R1 group	R2 group
Crocetin	H	H
1) Crocin-1 or α-crocin	A	A
2) Crocin-2 or tricrocin	A	B
3) Crocin-3	A	H
4) Crocin-4	H	B
5) Crocin-5 or dicrocin	B	B
1) Crocin-1 or α-crocin	A	A
2) Crocin-2 or tricrocin	A	B

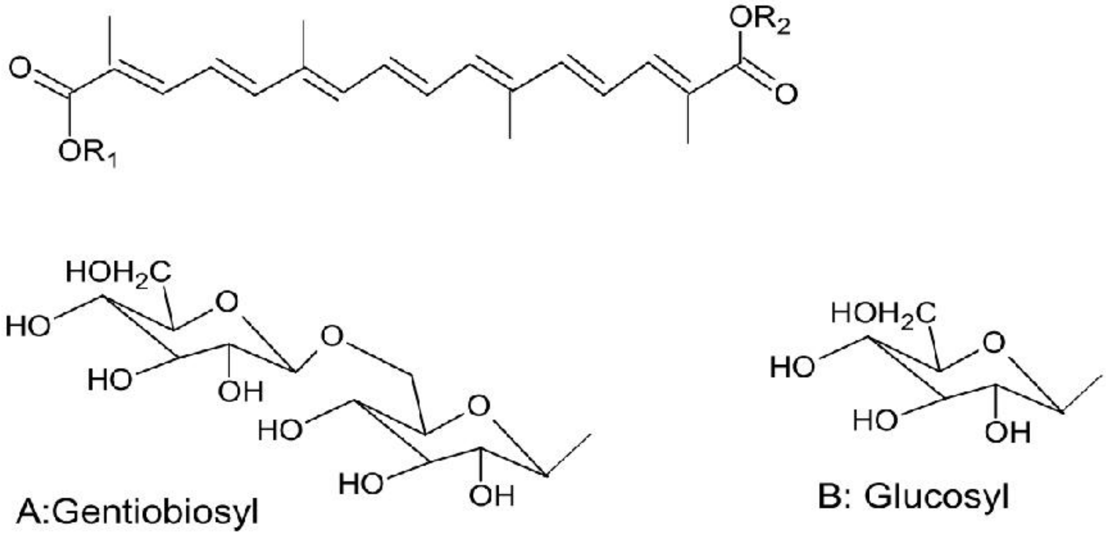

Figure 1: Molecular structures of crocetin with gentiobiosyl (A) and glucosyl (B) radicals. The main crocins esters of crocetin are: 1) digentiobioside crocetin; 2) gentioglucoside crocetin; 3) glucoside crocetin; 4) glucoside crocetin; 5) diglucoside crocetin (see Tab 1).

4 Antioxidant activity of saffron

The main biological activity of saffron is based on its great antioxidant ability; In fact, the antioxidant properties of saffron are well known and have been widely studied since this property is responsible for many of its biomedical attributes.

Many studies showed that different extracts of saffron of *Crocus sativus* demonstrate good antioxidants properties. The antioxidant activity of ethanolic and aqueous extracts of the stigmata and its main bioactive constituents, crocin and safranal, was evaluated by 3 different methods: the use of deoxyribose, lipid peroxidation of the erythrocyte membrane, and lipid peroxidation of non-enzymatic hepatic. The aqueous and ethanolic extracts at different concentrations (10, 100, 250, 500 and 1000 pg/ml), crocine and safranal at 0.1, 0.5, 1 and 2 mM were tested. The results showed that the test compounds may decrease the extent of the generation of MDA (3,4-methylenedioxyamphetamine). The effect of crocin at 1.2 mM and ethanolic extract at 500 and 1000 µg/ml on lipid peroxidation of microsomes in the liver were similar to that of the effect of 100 µM BHT (butylated hydroxytoluene: characterized by these antioxidant properties) (Hosseinzadeh et al., 2009).

This study showed that ethanolic and aquoues saffron extracts have antioxidant activity in several in vitro tests. Crocine, the major carotenoid of saffron may have a greater role for anti-oxidant properties. Safranal, a monoterpene aldehyde, which is the main constituent of saffron plant essential oil, has also shown antioxidant activity (Hosseinzadeh et al., 2009).

Other scientific studies suggest that the main active compounds of saffron can help slow the growth of cancer cells and also the appearance of tumors (tumorigenesis and carcinogenesis). And can also weaken the highly negative side effects of the anticancer drug Platinol (cisplatin) (Samarghandian and Borji, 2014). The effect of *Crocus sativus* compounds on cancer may be related to the antioxidant effect of saffron. A study that administered 50 mg of saffron dissolved in 100 ml of milk twice daily resulted in a noticeable decrease in lipoprotein oxidation in patients with coronary artery disease and enhanced the antioxidant power of saffron. Active substances of saffron, including carotenoids such as crocine, may be necessary to decrease the growth of cancer cells (Al-Snafi, 2016).

Conclusion: All cited studies showed that saffron extracts have high antioxidant activity due to their different constituents and active molecules, such as crocine and safranal.

5 Antibacterial activity of saffron

To estimate separately the antimicrobial activities of various total extracts and under fraction of *Crocus sativus*'s tepals and stamens against the microorganisms responsible for foodborne diseases). A study that was carried out on five microbial strains: Salmonella enterica, Staphylococcus aureus, Bacillus cereus, Shigella dysenteriae and Escherichia coli. To determine the potential for microbial activity. Using the diffusion method, minimum inhibitory concentration (MCI), and minimum bactericidal concentration (CMB), these values were determined by the macrodilution method. The experiment was based on the preparation of extracts and fraction of the tepals and stamens separately from the *Crocus sativus* plant, by maceration with methanol. After drying, the raw extracts were then extracted by chloroform, ethyl acetate, methanol and water. The solvents of the extract and fractions were removed under reduced pressure in a rotating evaporator until they became completely dry.

The results founded showed that methanolic extract of the tepals indicates significant antibacterial activity against E. coli, S. aureus, S. typhi. B. cereus, and S. dysenteriae with inhibition zone diameters ranging from 13 to 22 mm, while ethyl acetate fraction showed the best antibacterial activity against B. cereus with an inhibition zone diameter of 15 mm. Aqueous and chloroform fractions were less effective against the strains studied.

The ethyl acetate fraction of the C. sativus stamens has the best antibacterial activity on S. typhimirium, E. coli and S. dysenteriae with inhibition zone diameters ranging from 14 to 21 mm while the most active extract against B. cereus and S. aureus is the total extract (Nouioua and Sofiane, 2019).

In another study, to determine the antibacterial property of stigmas extract the researchers used four pathogenic bacterial strains (Staphylococcus aureus, E. coli, Pseudomonas aeruginosa and Shigella flexneri) using the diffusion method and minimum inhibitory concentration (MCI). The methanol stigma extract of saffron was found to be more effective in inhibiting all the pathogenic strains (Parray et al., 2014).

6 Antifungal activity of saffron

In order to determine the antifungal properties of the *Crocus sativus*, against infections from fungi that cause significant deterioration at the organ level. Two independent experiments based on the external freeze dried and sterilized parts (Pelage) and internal of the bulb of the strain.

Five fungi (Aspergillus niger, Bipolaris spicifera, Fusarium oxysporum, Penicillium raistriicki, Rhizopus nigricans) were isolated from infected bulbs in August.

The results showed that the minimum inhibitory concentrations (MCI) after 30 days of coat treatments were 5.4% against Aspergillus Niger, 3.9% against Bipolaris spicifera, Fusarium oxysporum, Penicillium raistriicki, and 2.3% against Rhizopus nigricans, while the internal IFC was not detected for A. Niger and B. spicifera; However, 7.0% against F. oxysporum and P. raistriicki and 3.9% against R. nigricans.

The higher toxicity of the outer part to fungi led researchers to study the influence of saponin (naturally produced molecules from plants or animals characterized by a toxicity property), which are only detected at the outer part of the corm, the main influence of these compounds on toxicity was against F. oxysporum, the most common pathogen in saffron bulbs, followed by B. spicifera and A. niger. Inhibition of growth of P. raistriicki and R. nigricans is almost negligible. However, other compounds such as phenolic compounds may also be responsible for the fungicide activity detected (Rubio-Moraga et al., 2013).

Conclusion: The results of this study provide evidence that C. sativus bulbs contain antifungal compounds that resist high temperatures. This resistance is higher in the outer part than in the inner part of the bulb. This could be an advantage to exploit this plant in the production of new phytochemicals with antifungal properties.

7 Therapeutic uses of saffron

Saffron or stigmas and their associated carotenoid ingredients are extensively studied for their biomedical properties, especially for their chemopreventive potential against cancer saffron and neurodegenerative diseases.

7. 1 Alzheimer's Disease

It is one of the neurodegenerative diseases, which causes the destruction of neurons, which leads to the progressive loss of memory.

To predict Alzheimer's disease in humans, different studies have been done by researchers on the action of saffron against different neurodegenerative diseases that indicate that saffron would be beneficial and have a real neuro-protective action. Indeed, researchers show that crocin is the active component of saffron used for therapeutic purposes) has a major role in stimulating and improving brain memory (Tamaddonfard et al., 2013, Bolhassani et al., 2014).

One study was carried out and consists of temporarily confiscating the oxygen brain, in order to promote a major oxidation reaction at the time of the return of oxygen, causing more or less extensive neurological damage.

Researchers have concluded that saffron causes protective effects and reduces brain damage. Also, It has been previously revealed that treatment by stigmas extract for three weeks could significantly improve cognition deficits induced by ICV injection of STZ in rats; Crocin (30 mg/kg) has also been shown to have an antagonizing effect on the STZ-induced cognitive deficits in rats (Khalili and Hamzeh, 2010, Khazdair et al., 2015).

7.2 Improvement of learning abilities and memory

The oral application of 125–500 mg/kg of saffron extract to mice had no effect on learning abilities in the passive avoidance test, but distinctly improved the memory of mice pre-damaged with ethanol. This effect could be attributed to crocin, which does not have an effect in a dose range of 50–200 mg in healthy animals, but in fact improves cognitive functions in animals where memory was artificially impaired by application of ethanol (Sugiura et al., 1995, Sugiura et al., 1994)

7.3 Depression

A mental state characterized by a pessimistic feeling of insufficiency and lack of discouraged activity, the people affected are sad and have no taste for anything and feel worthless. So the researchers have done different work on the action of saffron to carry out a prevention of depression. They are found that there is an action of saffron on depression, which comes particularly from crocin and safranal.

The conclusion is that these constituents (crocin and safranal) increase the concentration of the two pleasure hormones dopamine and serotonin in the brain, which reflects their preventive effect on depression (Hausenblas et al., 2013).

7.4 Multiple Sclerosis

Oxidation of low-density lipoprotein plays a crucial role in the pathogenesis of atherosclerosis, raising the possibility of using antioxidants as an inhibitor of atherosclerosis. Multiple sclerosis is a neurodegenerative disease of the central nervous system; it is characterized by loss of myelin it is an autoimmune disease.

Saffron is involved in the prevention of multiple sclerosis by its active component crocin, which helps prevent myelin making brain cells; Crocin and crocetin plays an essential role in the efficiency of electrical conduction of nerve stimulions in the central nervous system and peripheral nervous system. In vitro studies demonstrated that supplementation with crocetin significantly increased the resistance of LDL to cupric ion-induced oxidation which might result from an increased plasma antioxidant power, therefore, the suppression of LDL oxidation by crocetin contributes, at least partly, to the attenuation of atherosclerosis (Sheng et al., 2006).

Another paper presents the effect of ethanol extract of saffron in the treatment of Experimental Autoimmune Encephalomyelitis (EAE) in mice was evaluated. EAE was induced by immunization of 8 week old mice. Therapy with saffron was started on the day of immunization. In the end of treatment, saffron was significantly reduced the clinical symptoms in mice with EAE. Also, treated mice displayed a delayed disease onset compared with control mice. Typical spinal cord leukocyte infiltration was observed in control mice compared with saffron treated mice. These results suggest that saffron is effective in the prevention of symptomatic EAE by inhibition of oxidative stress and leukocyte infiltration to CNS and may be potentially useful for the treatment of Multiple Sclerosis (Ghazavi et al., 2009).

7.5 Saffron and cancer

Cancer is one of the most feared diseases globally and there has been a sustained rise in its incidence in both developing and developed countries. To struggle this killer disease, a relentless screening of superior and safer drugs has been underway for many decades, resulting in the detection of the anticancer properties of several phytochemicals. Chemoprevention using natural materials easily substances from vegetables, fruits, herbs and spices is one of the most important approaches to cancer prevention in the present age. Among the spices saffron has generated interest because his pharmacological properties.

Extract of saffron (Crocus sativus) inhibited colony formation and cellular DNA and RNA synthesis by HeLa cells in vitro (Aung et al., 2007).

The anti-proliferative effect of Crocus sativus extract and its major constituent, crocin, was studied on three colorectal cancer cell lines (HCT-116, SW-480, and HT-29). The cell growth inhibition effect was compared to that of non-small cell lung cancer (NSCLC) cells. In addition, Crocus sativus effect on non-cancer cells was also evaluated. Significant concentration-related inhibitory effects of the extract on all three colorectal cancer cell lines were observed ($p<0.01$). The proliferation was reduced most significantly in HCT-116 cells (to

45.5%) at 1 mg/ml and (to 6.8%) at 3 mg/ml. Crocin at 1 mM, significantly reduced HCT-116, SW-480, and HT-29 cell proliferation to 2.8%, 52%, and 16.8%, respectively ($p<0.01$). Since 3 mg/ml Crocus sativus extract contained approximately 0.6 mM crocin, the observed effects suggest that crocin was the major responsible constituent in the extract. Significant anti-proliferative effects were also observed in non-small cell lung cancer cells. However, Crocus sativus extract did not significantly affect the growth of non-cancer young adult mouse colon cells (Aung et al., 2007).

The potential of the ethanolic extract of saffron to induce antiproliferative and cytotoxic effects was tested in cultured carcinomic human alveolar basal epithelial cells in comparison with non-malignant (L929) cells. Both cells were cultured in Dulbecco's modified Eagle's medium and treated with the ethanolic extract of saffron at various concentrations for two consecutive days. The results showed that the ethanolic extract of saffron decreased cell viability in malignant cells in a concentration and time-dependent manner. The IC50 values against the lung cancer cell line were determined as 1500 and 565 µg/ml after 24 and 48 h, respectively.

However, the extract at different concentrations could not significantly decrease the cell viability in L929 cells. Morphology of MCF7 cells treated with the ethanolic extract confirmed the MTT results (Samarghandian et al., 2010).

The cytotoxic and apoptotic effects of the ethanolic extract of saffron were evaluated on carcinomic human alveolar basal epithelial cells (A549), a commonly used cell culture system for in vitro studies on lung cancer.

The cells were cultured in Dulbecco's modified Eagle's medium with 10% fetal bovine serum and treated with different concentrations of the ethanolic extract of saffron for two consecutive days. Cell viability was quantitated by the 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide assay. Apoptotic cells were determined using annexin V-fluorescein isothiocyanate by flow cytometry. Saffron decreased the cell viability in the malignant cells as a concentration- and time-dependent manner. The IC_{50} values against the A549 cell lines were determined as 1,200 and 650 µg/ml after 24 and 48 h, respectively (Samarghandian et al., 2010).

The cytotoxic effect of saffron extract was evaluated on HepG2 and HeLa cell lines. Malignant and non-malignant cells (L929) were cultured in DMEM medium and incubated with different concentrations of ethanolic saffron extract. Cell viability was quantitated by MTT assay. Apoptotic cells were determined using PI staining of DNA fragmentation by flow cytometry (sub-G1 peak). ROS was measured using DCF-DA by flow cytometry analysis. Saffron

decreased cell viability in malignant cells in a concentration and time-dependent manner. The IC50 values against HeLa and HepG2 were determined as 800 and 950 microg/ml after 48 h, respectively. Saffron induced a sub-G1 peak in flow cytometry histogram of treated cells compared to control, which indicated that apoptotic cell death was involved in saffron toxicity. This toxicity was also independent of ROS production (Tavakkol-Afshari et al., 2008).

The mutagenic, antimutagenic and cytotoxic effects of saffron and its main components were studied on the growth of different human malignant cells in vitro. Colony formation assay was used to determinate the cytotoxic activity of saffron extract and its components on human tumor cells in vitro. Mutagenicity and antimutagenicity assays were performed by the Ames method. Saffron was non-mutagenic, non-antimutagenic and non-comutagenic. Saffron extract itself and some of its ingredients displayed a dose-dependent inhibitory activity against different types of human malignant cells in vitro. HeLa cells were more susceptible to saffron than other tested cells (Abdullaev et al., 2002).

8 Saffron and urino-genital diseases

8.1 Sexual Disorders

Several men and women suffer from sexual illnesses such as erectile dysfunction, sexual dysfunction, sexual desire and sexual aversion disorders. To analyze the effects of saffron on sexual dysfunction and sperm mobility. Studies show that a daily dose of 30 mg of saffron can improve the sexual function of men and women with sexual dysfunction (Modabbernia et al., 2012). Studies of erectile dysfunction (ED) in humans have shown that saffron has produced positive results in the treatment of erectile dysfunction; 20 male patients with ED were followed for 10 days in which each morning they took a tablet containing 200 mg of saffron.

The results showed a significant improvement in erections in terms of frequencies, qualities, rigidities for objective criteria. Positive results were mentioned for subjective criteria such as: increase sexual desire, pleasure, number and duration of erectile events and improvement of orgasmic function. So, we can conclude that extract of red stigma has some good aphrodisiac properties (Shamsa et al., 2009).

8.2 Menstrual Disorders

In a recent study, the scientists tested the effects of saffron on symptoms unique to Thirty-five healthy women, such as premenstrual syndrome, menstrual pain and irregular menstruation. In the end of experiment, the levels of cortisol (C), testosterone (T) and 17-β estradiol (E) was measured. They found that stigmas of saffron significantly decreased C levels after short-term stimulation (20 min) in both follicular and luteal phases. E level after exposure to saffron odor was increased in both the follicular- and luteal-phase groups. The present findings indicate that saffron odor exert some impacts (physiological and psychological effects) in the treatment of premenstrual syndrome, menstrual pain and irregular menstruation, and may be effective in treating menstrual distress (Fukui et al., 2011).

8.3 Absence/weakness of fertility

In order to increase fertility in humans, the researchers have carried out several studies on the effect of saffron on the stimulation of fertility; These studies show that saffron increases the number, motility and morphological components of sperm. Thus, for the improvement of fertility in humans, it is necessary to consume 50 mg of saffron 3 times a week until positive results are achieved (Maleki-Saghooni et al., 2018). Other studies have been carried out on the effectiveness of saffron on increased fertility, which concludes that saffron is effective for the increase of sexual hormones (LH, FSH and testosterone) (Maleki et al., 2016). So we can conclude that saffron has a positive effect on erectile dysfunction. However, the investigation showed the good effect of extract of stigma on qualities, rigidities and sexual dysfunction; also, on the premenstrual syndrome, menstrual pain and increase number, motility and morphological components of sperm.

9 Conclusions

The use of saffron for food coloring and flavoring by the general public is widely accepted throughout the world and by many cultural groups. However, scientists worldwide are more attracted to saffron's potential for biological or pharmacological function, which may be attributed to the large number of phytochemicals found in saffron. The present review article discusses the chemical constituent, pharmacological and therapeutic effects of *Crocus sativus* as promising source of many drugs because of its safety and effectiveness. All cited studies, clearly indicate that consumption of

saffron can be potentially useful in prevention of metabolic disorders and positively correlates with a lower risk of diseases and healthy disorders.

10 Conflicts of Interest

The authors declare no conflict of interest.

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