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Saffron (*Crocus sativus* L.): A Review of its Ethnopharmacological value

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ABSTRACT

Saffron (*Crocus sativus* L.) is widely used as drug to promote health and fight disease from ancient time. In countries like India and other Asian countries, saffron is used very frequently in various alternative systems of medicine including Unani System of Medicine, Ayurveda and Traditional Chinese Medicine, as it is considered bitter, acrid, fragrant, stimulant, tonic, stomachic, aphrodisiac, anodyne, antispasmodic, emmenagogue, diuretic, laxative, galactagogue and is useful in bronchitis, pharyngopathy, cephalgia, vomiting, fever, melancholia, hepatomegaly etc. Because of its wide range of medical uses in traditional systems of medicine, the saffron has under gone extensive phytochemical and biochemical studies and some of the studies have shown that number of constituents including Crocin, Crocetin, Safranal are present, out of which crocetin is mainly responsible for pharmacological actions. This paper is an attempt to review the saffron on the basis of Unani System of Medicine and to discuss its recent phytochemical and pharmacological studies.

Keywords: Saffron, Unani System of Medicine, Phytochemicals, Pharmacological actions.

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INTRODUCTION

Saffron is the dried stigmas and upper part or top of the styles of *Crocus sativus* L. It is the world's most expensive spice and genuine saffron is worth its weight in gold. This plant belongs to the Iridaceae family ^{1, 2, 3, 4} among the 85 species belonging to the *Crocus* genus, saffron is the most fascinating and intriguing spice ⁵.

As a medicinal plant saffron has traditionally been considered as anodyne, antidepressant, respiratory decongestant, antispasmodic, aphrodisiac, diaphoretic, emmenagogue, expectorant, sedative. Used in scarlet fever, small pox, colds, asthma, heart diseases, tumour, cancer, flatulent colic and in menstrual disorders ^{6, 7} and because of all these actions and uses saffron is included in various Unani and Ayurvedic polyherbal formulations.

Modern pharmacological studies have demonstrated that saffron extracts have antinociceptive, anti-inflammatory, antitumour, radical scavenger, anticonvulsant, hypolipidemic, hypocholesterolemic activity. Studies have shown that number of constituents including Crocin, Crocetin, Safranal are present, out of which crocetin is mainly responsible for pharmacological actions ^{8, 9}.

Historical background

It is used for depression in Persian traditional medicine. Indeed, it is a Persian herb with a history as long as the Persian Empire itself. Iran at present is the world's largest producer of saffron ¹⁰. The Mediterranean region is one of the probable sites of the origin of the saffron. Another site could be in the East in Turkey, Iran and India where saffron cultivation is reported to be thousands of years old. According to some authors the saffron first originated in Iran and Kashmir from where Phoenicians introduced it to Greek and Roman world. Later it was brought by Arabs and Moors to the Spain ¹¹. As far as Kashmir is concerned, it is thought that the saffron cultivation started in the reign of king Lalitaditya during 550 A.D. In "Tozaki-jahangari" some reference has been made regarding saffron, that Kashmiri vaids used saffron as an ingredient of fragrance, as dye and in herbal medicine ¹².

The word saffron is derived from the Arabic word za'fraan, which translates to yellow ⁵. The term in ancient Greek is Korikos, the Romans used the term *Crocum*; English, Saffron; Italian, Zafferano; French, safran; Spanish, Azafran; German, Saffran; Russian, Shafran; Turkish, Zaferan ^{11, 13}. In Sanskrit it bears the name of kumkuma and is described as charu (fair), vara (suitor), agnishikha (having a crest of fire), saurabh (fragrant) ¹⁴.

Saffron in different civilizations

The first unarguable reference to its use is by the Minoan civilization. That civilization developed on the island of Crete and was a forerunner of Greek civilization. The English archaeologist Sir Arthur John Evans discovered some frescoes on the archaeological site of the palace of Knossos, dating from 1600 B.C. that represent a blue figure gathering whole Crocus plants. In another later fresco, (1500 B.C.) found on the Isle of Thera (now Santorini), some youths are seen collecting just the stigma of the flower.

In the 5th Century A.D. to 15th Century A.D., the main European saffron trading centre was Venice and the most important buyers were German. At that time, in Venice, there was an armed guard called *Ufficio dello zafferano* whose duty it was to inspect the saffron traders and avoid possible forgery or adulteration. In 1358, a law known as Safranschau” was enacted in Nuremberg. This was one of the first known laws on food and exclusively concerned the quality of commercial saffron. The law provided for capital punishment in certain cases and several people were even executed by being burned alive with their adulterated products ¹⁵. Magic properties are ascribed to the Saffron in Persia, Haji Zain el Attar states that it is called Jadu-i-dikhan “peasant’s magic” and that pregnant women wear a ball of it, about the size of the walnut at the pit of the stomach to ensure speedy delivery and expulsion of the afterbirth. The Arabs believe that the saffron will drive away the lizard called Sam abras which they greatly dread ¹⁴.

Saffron in Holy Books

Saffron is also mentioned in the Holy Quran ¹⁶ and the Holy Bible ¹⁷.

Botanical Description

A perennial herb with a solid depressed globular corm about an inch in diameter, giving off from its under surface several slender whitish roots, covered with a thin coating of several layers of fine longitudinal pale brown fibres and producing on the top one or more buds.

Leaves: leaves produced from the new bud, few (6-9) very closely placed, sessile, forming an erect tuft, 4-6 inches long, linear, acute, entire, stiff, curved outwards, smooth shining deep green, with a white depressed midrib.

Flowers: Flowers axillary with a 2 valved membranous spathe, appearing with the leaves, large, purple, and striated with a campanulate limb.

Corolla: Corolla in two segments, between which the long styles hang out.

Style: Style very long and slender, colourless in the perianth tube, which it exceeds, dividing at the level of the anthers into 3 yellow drooping branches which hang out of the flower and become gradually thickened and tubular upwards.

Anther: Anthers linear, longer than the filaments, sagittate at the base and bright yellow ^{1, 18, 19}.

Stigmas: The dried Stigmas are the “Saffron of the Shops”;¹⁸

Macroscopic characters of Stigma:

1. Colour- Stigma dark red to reddish brown.
2. Odour- Strong, characteristic and aromatic
3. Taste- Characteristic and bitter
4. Size- 25mm long
5. Shape- Trifid²

Microscopic characters of Stigma:

Stigma mainly composed of elongated thin walled parenchyma cells containing coloring matter, at the upper end numerous cylindrical papillae or trichomes up to 150 μ long, pollen grains few, spherical, nearly smooth, from 40 μ to 120 μ in diameter, occasionally germinated and exhibiting pollen tubes²⁰.

Habitat:

Saffron is a native of Southern Europe and cultivated in Mediterranean countries, particularly in Spain, Austria, France, Greece, England, Turkey, and Iran. In India, it is cultivated in Jammu & Kashmir and in Himachal Pradesh¹³.

Time and method of planting:

The most appropriate time of planting the saffron corm is the second fortnight of August. A spacing of 5cm X 15 cm requiring 40 quintals of seed corms/hectare is best for optimum yield. The corm should be planted 15-22 cm deep in the soil. Saffron corms planted once, last for 6-7 years before the plantation becomes uneconomical²¹.

1. Heavy to very heavy rainfall is not suitable for Saffron production.
2. A decrease in relative humidity below 65 % reduces the production of Saffron.
3. The optimum range of temperature for Saffron production is between 20 °C to 22 °C²².

Harvesting and Processing

Picking of the flowers is done during morning hours in November and December and it has been found most suitable for obtaining optimum yield. The stigma along with the style is pinched off from the harvested flowers immediately and subjected to air drying^{2,21}. Drying experiments show that drying at temperatures up to 110°C can be used. The critical issue is the length of drying time (e.g. at 110°C for 2 minutes). Recent Spanish research shows drying in a hot air flow at 70°C for 6 minutes will give quality saffron. Brightness of colour is aided by quick high temperature drying. Slow drying gives a poor-quality product. Another method is to use a dehydrator at 48°C for 3

hours. Irrespective of the drying method, it is important not to over dry. A final dry matter close to 10% moisture is adequate for long-term storage ²³.

Phytochemical Studies

The stigmas of the saffron flower contain many chemical substances. Carbohydrates, minerals, mucilage, vitamins and pigments, amino acids, proteins, starch, gums, and other chemical compounds have also been described in saffron ⁶. Saffron contains more than 150 volatile and aroma-yielding compounds and most of volatile oils are composed of esters, terpenes and terpene alcohol ^{24, 25}.

Carbohydrates: Glucose, fructose, gentibiose and small quantity of xylose and ramnose ²⁶.

Minerals: International standard organization reported that the total weight of different elements in 100 g of dried saffron as: calcium 111 mg, phosphorous 525 mg, potassium 1724 mg, sodium 148 mg, zinc and magnesium in small quantities ²⁶.

Vitamins: Thiamine and Riboflavin ²⁶

Pigments: Crocin, anthocianin, α -carotene and β -carotene, lycopene, zigzantin, flavonoids ⁶.

Complete analysis of Saffron: ²⁴

Proximate analysis of Saffron		Proximate analysis of Saffron	
Component	Mass %	Component	Mass %
Water-soluble components	53.0	Lipids	12.0
Gums	10.0	Non-volatile oils	6.0
Pentosans	8.0	Volatile oils	1.0
Pectins	6.0	Protein	12.0
Starch	6.0	Inorganic matter("ash")	6.0
α -Crocic	2.0	HCl-soluble ash	0.5
Other	1.0	Water	10.0
carotenoids			
Fiber (crude)	5.0		

The saffron stigma, which is what basically forms commercial saffron, has a distinct and unique color, flavour and aroma and some of the groups of chemical compounds responsible for each of these properties have now been identified.

The color of saffron

Crocic (C₄₄ H₆₄ O₂₄) is the most influential chemical in the colouring power of saffron. It is a rare carotenoid found in nature which can easily dissolve in water. In comparison to other carotenoids, crocic has a wider application as a colorant in food and medicine, mainly because of its high solubility. This substance was first discovered by Solomon and Carrar in crystal form ^{26, 27}.

The taste of saffron

A glucose known as picrocrocin (C₁₆ H₂₆ O₇) is the major factor for the bitter taste of saffron. This bitter substance can undergo crystallization, through acid hydrolysis, producing safranal (a glucose and aldehyde) ²⁶.

The aroma of saffron

The main aroma factor in saffron is safranal, which 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 ⁶.

Pharmacological actions of Saffron in Unani System of Medicine

1. Majalli Basr (Improves eyesight) ^{28, 29, 30, 31, 32, 33}
2. Muhallil (Resolvent) ^{28, 29, 30, 31, 32, 33, 34}
3. Mufarreh (Exhilarant) ^{20, 29, 30, 32, 33, 34}
4. Mufatteh (Deobstruent) ^{29, 30, 32, 33, 34, 35}
5. Mudirre Baul (Diuretic) ^{20, 29, 30, 31, 32, 33, 34, 35}
6. Muharrike Bah (Sexual Stimulant) ^{20, 31, 32, 34}
7. Muqawwie Jigar (Liver tonic) ^{32, 33, 34}
8. Muqawwie Alaate Tanaffus (Tonic to respiratory organs) ^{30, 32, 33}
9. Qabiz (Astringent) ^{29, 31, 32, 33, 35}
10. Muqawwie Meda (Stomachic) ^{20, 32, 33}
11. Mulaiyin (Aparient) ³³
12. Munzij (Coctive) ^{31, 32, 33}
13. Muqawwie Ahsha (Tonic to visceral organs) ^{29, 30, 32, 33, 34, 35}
14. Muhallile Riyah (Carminative) ³⁰
15. Mudirre Haiz (Emmenagogue) ^{20, 29, 30, 33}
16. Mugharri (Agglutinant) ^{31, 32}
17. Musakkin (Sedative) ^{20, 30}
18. Muqawwie Qalb (Cardiotonic) ^{29, 30, 31, 32, 33}
19. Protect the humors from putrefaction ^{29, 30, 31, 32, 33}
20. Skin Whitener ^{30, 31}
21. Dafaе Tashannuj (Antispasmodic) ²⁰
22. Muqawwie Reham (Uterine Tonic) ²⁰
23. Muqawwie Dimagh (Brain Tonic) ³³
24. Munaqqie Gurda wa Masana ^{30, 33, 34}

Pharmacological Studies

Anti-Alzheimer Activity:

The main carotenoid constituent, trans-crocin-4, the digentibiosyl ester of crocetin, inhibited A-beta fibrillogenesis in Alzheimers disease. The water: methanol (50:50, v/v) extract of *Crocus sativus* stigmas inhibited A-beta fibrillogenesis in a concentration and time dependent manner at lower concentrations than it's another constituent dimethylcrocetin ¹⁹.

Anti Depressant Activity:

The efficacy of petal of *Crocus sativus* is compared with stigma of *Crocus sativus* in the treatment of depressed outpatients. In this double-blind and randomized trial, patients were randomly assigned to receive capsule of petal of *Crocus sativus* 15 mg bid (morning and evening) (Group 1) and capsule of stigma of *Crocus sativus* 15 mg bid (morning and evening) (Group 2) for a 6-week study. At the end of trial, petal of *Crocus sativus* was found to be effective similar to stigma of *Crocus sativus* in the treatment of mild to moderate depression (d.f.=1, F= 0.05, P=0.81) ³⁶.

The efficacy of the stigmas of *Crocus sativus* was assessed in the treatment of mild to moderate depression. In this trial, patients were randomly assigned to receive a capsule of saffron 30 mg/day (BD) (Group 1) or a capsule of placebo (BD) (Group 2) for a 6-week study. At 6 weeks, *Crocus sativus* produced a significantly better outcome on the Hamilton depression rating scale than the placebo (d.f. = 1, F = 18.89, p < 0.001) ³⁷.

The efficacy of hydro-alcoholic extract of *Crocus sativus* (stigma) is compared with fluoxetine in the treatment of mild to moderate depression. In this trial, patients were randomly assigned to receive capsules of saffron 30 mg/day (BD) (Group 1) and capsule of fluoxetine 20 mg/day (BD) (Group 2) for a 6-week study. Saffron at this dose was found to be effective similar to fluoxetine in the treatment of mild to moderate depression ³⁸.

Anti-diabetic activity:

Crocetin, the active constituent of saffron was found to possess anti diabetic activity in fructose-fed rats as it alleviated free fatty acid induced insulin insensitivity and dysregulated mRNA expression of adiponectin, TNF-alpha and leptin in primary cultured rat adipocytes suggesting the possibility of crocetin treatment as a preventive strategy of insulin resistance and related diseases ¹⁹.

Anti Gastric Ulcer activity:

An aqueous suspension of saffron was subjected for evaluating gastric antiulcer activity in rats. The saffron aqueous suspension at doses (250 and 500 mg kg⁻¹) exhibited decrease in basal gastric secretion and ulcer index in Shay rats and indomethacin treated groups. Gastric wall mucus elevation was observed. No significant histopathological changes were noted. Saffron exhibited

significant antisecretory and antiulcer activities without causing any deleterious effects on acute and chronic toxicity in rodents ⁷.

The effects of the ethanol extract of saffron and its active constituents crocin and safranal are compared with omeprazole against gastric ulcer induced by indomethacin in non-diabetic and streptozocin diabetic rats were studied. The effects of saffron extract, crocin and safranal on the gastric ulcer index, lipid peroxidation and glutathione levels were comparable to omeprazole ³⁹.

Anti Parkinson's Activity:

In experimental rats, pre-treated with crocetin, there was an increase in the antioxidant capacities of enzymes followed by protection from the deleterious effects of 6-hydroxy dopamine thus presenting itself as a good treatment to combat the Parkinson's disorder ^{5, 12, 19}.

Anti-pruritic and Emollient effects:

Crocus sativus in a topical formulation at a concentration of 0.025%v/w was found to have beneficial effects, with atopic dermatitis, ichthyosis vulgaris, and other xerotic diseases of mild severity ¹⁹.

Antiatherosclerosis Effect:

Recently it was demonstrated that suppression of LDL oxidation by crocetin contributes to the attenuation of atherosclerosis ⁵.

Anticonvulsant activity:

The anticonvulsant activities of *C. sativus* stigma constituents, safranal and *crocin*, were evaluated in mice using pentylenetetrazole (PTZ)-induced convulsions in mice. Safranal (0.15 and 0.35 ml/kg body weight, i.p.) reduced the seizure duration, delayed the onset of tonic convulsions, and protected mice from death. Crocin (22 mg/kg, i.p.) did not show anticonvulsant activity ⁴⁰.

The anticonvulsant activity of the aqueous and ethanolic extracts of *Crocus sativus* stigma is studied in mice. In the Pentylenetetrazole test, CSS delayed the onset of tonic convulsions, but failed to produce complete protection against mortality. In the Maximal electroshock seizure test, both extracts decreased the duration of tonic seizures. The results of this study indicate that the extracts of CSS may be beneficial in both absence and tonic clonic seizures⁴¹.

Antihyperlipidemic activity:

Crocin, one of the constituents of saffron was shown to produce hypolipidemic effect in the dose range of 25 mg/kg to 100 mg/kg body weight in diet-induced hyperlipidemic rats by inhibiting pancreatic lipase thereby leading to malabsorption of fat and cholesterol producing hypolipidemic effect ¹⁹.

Antihypertensive Activity:

The effects of saffron (*Crocus sativus*) stigma aqueous extract and two active constituents, crocin and safranal, were investigated on blood pressure of normotensive and desoxycorticosterone acetate-induced hypertensive rats. The aqueous extract of saffron stigma, safranal and crocin reduced the MABP (Mean Arterial Blood Pressure) in normotensive and hypertensive anaesthetized rats in a dose-dependent manner⁴².

The effects of *C. sativus* petals' extract were investigated on blood pressure in anesthetized rats and also on responses of the isolated rat vas deferens and guinea -pig ileum induced by electrical field stimulation (EFS). Aqueous and ethanol extracts of *C. sativus* petals' reduced the blood pressure in a dose-dependent manner⁴⁰.

Antinociceptive and anti-inflammatory Activity:

The antinociceptive activity of the *Crocus sativus* was evaluated by using the aqueous and ethanolic maceration extracts of stigma and petals. The effect of extracts against acute inflammation was studied using xylene induced ear edema in mice. The activity of the extracts against chronic inflammation was assessed by formalin-induced edema in the rat paw. In the hot plate tests, intraperitoneal injection of both extracts showed no significant antinociceptive activity in mice. The extracts exhibited antinociceptive activity against acetic acid induced writhing. Only the stigma extracts showed weak to moderate effect against acute inflammation. In chronic inflammation, both aqueous and ethanolic stigma extracts, as well as ethanolic petal extract, exerted anti-inflammatory effects⁴³.

Antioxidant Activity:

The methanolic extract of *Crocus sativus* and its components such as safranal, crocin etc. were reported to possess radical scavenging activity, suggesting its use as a cosmetic to treat age related disorders, as a food supplement etc¹⁹.

Fifty milligrams of saffron dissolved in 100 ml of milk was administered twice a day to human subjects and the significant decrease in lipoprotein oxidation susceptibility in patients with coronary artery disease (CAD) indicates the potential of saffron as an antioxidant¹².

Antitumor Activity:

The oral administration of the saffron ethanolic extract increased the life span of Swiss albino mice intraperitoneally transplanted with sarcoma-180 (S-180) cells, Ehrlich ascites carcinoma (EAC) or Dalton's lymphoma ascites (DLA) tumors. The authors did not identify the exact nature of the active compound from saffron stigmas, but suggested that this compound showed the presence of glycosidic linkage. Liposome encapsulation of saffron effectively enhanced its antitumor activity

against S-180 and EAC solid tumors in mice, promoting significant inhibition in the growth of these tumors ⁶.

Oral administration of saffron extract induced a dose-dependent inhibition of the growth in mice of ascite tumours ²⁴.

Antitussive Activity:

The antitussive activity of *C. sativus* stigma and petal extracts and its components, safranal and crocin, was evaluated using the nebolized solution of citric acid 20% in guinea pigs. The ethanolic extract of *C. sativus* (100-800 mg/kg) and safranal (0.25-0.75 ml/kg) reduced the number of cough. The ethanolic and aqueous extracts of petal and crocin did not show antitussive activity ⁴⁰.

Anxiolytic Activity:

The crocins were evaluated in rodents for the presence of anxiolytic properties. For this aim, the light\dark test was selected. Either crocins, at a dose which did not influence animals' motor activity (50 mg/kg), or diazepam (1.5 mg/kg), increased the latency to enter the dark compartment and prolonged the time spent in the lit chamber in the rats. Conversely, lower doses of crocins (15-30 mg/kg) did not substantially modify animals' behavior. The present results indicate that treatment with these active constituents of *C. sativus L.* induces anxiolytic-like effects in the rat ⁴⁰.

Cardiovascular activity:

Crocins inhibited an increase in serum triglycerides, total-, LDL-, cholesterol compared to the control group as seen before; however, the results also showed a significant increase in the fecal excretion of fat and cholesterol in the crocin group (100 mg/kg/day) ⁴⁴.

In another study, crocetin by virtue of its strong antioxidant activity prevented the cardiac hypertrophy induced by norepinephrine by increasing the levels of the antioxidant enzymes such as myocardial superoxide dismutase, catalase, glutathione peroxidase and also significantly improved the myocardial pathological histological changes induced by norepinephrine ¹⁹.

Antigenotoxic and Cytotoxic Activity:

The antimutagenic, comutagenic and cytotoxic effects of saffron and its main ingredients were assessed. When only using the TA98 strain in the Ames/*Salmonella* test system, saffron showed non-mutagenic, as well as non-antimutagenic activity against BP-induced mutagenicity, and demonstrated a dose-dependent co-mutagenic effect on 2-AA-induced mutagenicity. The saffron component responsible for this unusual comutagenic effect was safranal. In the in vitro colony formation test system, saffron displayed a dose-dependent inhibitory effect only against human malignant cells. All isolated carotenoid ingredients of saffron demonstrated cytotoxic activity

against in vitro tumor cells. Overall, these results suggest that saffron itself, as well as its carotenoid components might be used as potential cancer chemopreventive agents ⁴⁵.

The cytotoxic effect of aqueous extract of saffron is evaluated on human transitional cell carcinoma (TCC) and mouse non-neoplastic fibroblast cell lines. The cell lines were cultivated and incubated with different concentrations of aqueous extract of saffron stigma (50 µg/mL to 4000 µg/mL). After 120 hours, decrease in the percentage of survived cells at higher concentrations of saffron extract was seen in both cell lines this shows that Saffron aqueous extract has inhibitory effects on the growth of both TCC 5637 and normal L929 cell lines ⁴⁶.

Effect on Learning and Memory Behaviour:

The extract of saffron and two of its main ingredients, crocin and crocetin, improved memory and learning skills in ethanol-induced learning behavior impairments in mice and rats. Oral administration of saffron may be useful in the treatment of neurodegenerative disorders and related memory impairment ^{5,40}.

Effect on Premenstrual syndrome:

A study was conducted to investigate whether saffron (stigma of *Crocus sativus* L.) could relieve symptoms of premenstrual syndrome (PMS). Women aged 20–45 years with regular menstrual cycles and experience of PMS symptoms for at least 6 months was taken for the study. Women were randomly assigned to receive capsule saffron 30 mg/day (15 mg twice a day; morning and evening) (group A) or capsule placebo (twice a day) for a two menstrual cycles (cycles 3 and 4). In this trial, saffron was found to be effective in relieving symptoms of PMS ⁴⁷.

Effect on Respiratory system:

The relaxant effect of *Crocus sativus* on smooth muscle was evident as shown in guinea pig tracheal chain experiment. The relaxation produced with the aqueous-ethanolic extract and safranal in comparison with saline as negative control, and theophylline, was comparable to or even higher than that relaxation produced with theophylline suggesting its use in the treatment of various respiratory disorders like asthma etc ¹⁹.

Abortifacient Activity:

A study was conducted to evaluate the effect of saffron on abortion and its side effect on mice balb/c . The first group (case) was fed with saffron. The second group (control) was fed with water. Data were analyzed by odds- ratio with $P < 0.05$ as the limit of significance. Results: The results indicated that the percent of absorbed and abnormal embryos were increased significantly in the group that treated with saffron but fibrous and teratum sacrum wasn't significantly different

⁴⁸.

Effects on ocular blood flow and retinal function:

Crocin analogs isolated from saffron significantly increased the blood flow in the retina and choroid as well as facilitated retinal function recovery and it could be used to treat ischemic retinopathy and/or age-related macular degeneration^{5, 40}.

Effects on Sexual Behaviour:

The effect of *Crocus sativus* (saffron) was studied on male erectile dysfunction (ED). Twenty male patients with ED were followed for ten days in which each morning they took a tablet containing 200 mg of saffron. After the ten days of taking saffron there was a statistically significant improvement in tip rigidity and tip tumescence as well as base rigidity and base tumescence⁴⁹.

The aphrodisiac activities of *C. sativus* stigma aqueous extract and its constituents, safranal and crocin, were evaluated in male rats. Safranal did not show aphrodisiac effects. This study exhibited an aphrodisiac activity of saffron aqueous extract and its constituent crocin⁴⁰.

A clinical trial has been conducted in which 52 non smoker infertile men were enrolled. They were treated by saffron for 3 months. Saffron, 50 mg, was solved in drinking milk and administered 3 times a week during the study course. Semen analysis was done before and after the treatment and the results were compared. The mean percentage of sperm with normal morphology was $26.50 \pm 6.44\%$ before the treatment which increased to $33.90 \pm 10.45\%$. The mean percentage of sperm with Class A motility was $5.32 \pm 4.57\%$ before and $11.77 \pm 6.07\%$ after the treatment. No significant increase was detected in sperm count; the mean sperm count was $43.45 \pm 31.29 \times 10^6/\text{mL}$ at baseline and $44.92 \pm 28.36 \times 10^6/\text{mL}$ after the treatment period ($P = .30$). Hence it is concluded that Saffron, as an antioxidant, is positively effective on sperm morphology and motility in infertile men, while it does not increase sperm count⁵⁰.

Hepatoprotective activity:

Male Wistar rats (200-250g) were treated with saffron (40 or 80 mg/k/d) for 10 days and gentamicin 80 mg/kg/d for five days, starting from day 6. At the end of treatment, blood samples were taken for measurement of serum creatinine (SCr) and BUN. The left kidney was prepared for histological evaluation and the right kidney for Malondialdehyde (MDA) measurement. Gentamicin 80 (mg/k/d) increased SCr, BUN and renal tissue levels of MDA and induced severe histological changes. Saffron at 40 mg/k/d significantly reduced gentamicin-induced increases in BUN and histological scores ($p < 0.05$). Gentamicin-induced increases in BUN, SCr and MDA and histological injury were significantly reduced by treatment with saffron 80 mg/k/d ($p < 0.05$, $p < 0.001$, $p < 0.05$, and $p < 0.001$ respectively)⁵¹.

Radical Scavenging Activity:

The DPPH radical scavenging activity of extract of *Crocus sativus* L. (saffron), and some of its bioactive constituents (crocin, safranal) was studied. Crocin showed high radical scavenging activity (50% and 65% for 500 and 1000 ppm solution in methanol, respectively), followed by safranal (34% for 500 ppm solution). All the tested samples showed high radical scavenging activity, probably due to the ability to donate a hydrogen atom to the DPPH radical ⁵².

Relaxant Activity:

The effects of aqueous ethanolic extract of *Crocus sativus* were studied on the tracheal chains of guinea-pigs for its relaxant activity. The relaxant effect of the extract may be due to the safranal present in the *Crocus sativus*. The results indicated that safranal was, at least in part, responsible for the relaxant effect of *Crocus sativus* ^{24, 40}.

Wound healing Activity:

The study was conducted to evaluate the efficacy of pollen of saffron extract cream in the treatment of thermal induced burn wounds and to compare its results with silver sulfadiazine (SSD) in rats. Animals were divided into four groups and administered a topical cream including control, base, saffron (20%) or SSD (1%) at 24 hour after a burn injury that was induced by hot water. On day 25, average size of wound was 5.5, 4, 0.9 and 4.1 cm² in control, base, saffron and silver groups. Histological comparison has shown that saffron significantly increased re-epithelialization in burn wounds ⁵³.

Antimicrobial Activity:

Antimicrobial activity of different parts of *Crocus sativus* L. (saffron) including stigma, stamen, leaves and colour, extracted by various solvents, were tested against different bacteria and fungi by cup plate diffusion method. Minimal Inhibitory Concentration (MIC) values of each active extract were determined. The results obtained show strong activity of the ethyl acetate extract of various plant parts of the plant (except leaves) against bacteria and fungi used as test organisms ⁵⁴.

Toxicity

1. Muqi (Emetic) ^{30, 31, 34}
2. Muzife Ishteha (Decreases appetite) ^{31, 32, 34}
3. Musda'a (Cephalgic) ^{31, 32}
4. Muzirre Kulliya (Adverse effect on Kidneys) ^{29, 30, 34}
5. Muzife Riya (Higher doses show adverse effects on lungs) ³⁰.
6. At a high dose, saffron has narcotic and ecstasy effect and excessive delight which finally lead to temporary paralysis. Abortion at overdosing with high risk of maternal death is reported ²⁶.

7. The oral LD₅₀ of saffron is 20.7 g/kg administrated as a decoction ⁶.

Adulteration and fraud

In 2002, Safinter S.A. drafted a bibliographic study of saffron adulterations in history. This resulted in reference to more than 120 substances used at some time in history to forge or adulterate saffron ¹⁵. Saffron is frequently adulterated with styles, anthers and parts of corolla of saffron. In India it is commonly adulterated with florets of safflower botanically known as *Carthamus tintorius* Linn. family Compositae, which are orange in colour. Safflower florets impart orange colour to alcohol, whereas no colour is observed with authentic drug. The weight of the drug is sometime increased by addition of glycerine and ammonium nitrate ^{2, 55}.

Some points which can distinguish between the false or adulterated product and the genuine one.

- Saffron should not be sticky or soft to the touch, and even more so when some months have elapsed from it being packed.
- Whenever possible, the stigmas must be joined together by the style (except for *coupé* saffron: which is saffron cut at, about 10-15 mm to completely eliminate the style).
- The part that joins the stigmas and which ends in a filament is called style. The style is yellowy white so, if it is red after the joint, it has been dyed.
- The stigmas must have a length between 2 and 4 cm and the colour must be dark red.
- If small pink stains, crystals or shiny material is found, it is an unmistakable sign that the product has been adulterated.
- If the saffron tastes salty or sweet when tried, it has been adulterated.
- If there are doubts concerning whether the product has been adulterated, or is completely false, one may proceed to submerge the filaments in cold water or milk and the dye colour will be quickly released. Genuine saffron will only colour water or milk when these are hot and after a few minutes ¹⁵.

Chemical test:

Add a drop of sulphuric acid to the dry stigma. It turns blue, gradually changing to purple and finally purplish-red ⁵⁵.

CONCLUSION

This review describes the complete information about various aspects of *Crocus sativus*, these include description, habitat, botanical description, the Unani pharmacological as well as recent studied pharmacological actions and phytochemical studies. However, as saffron and its constituents show a wide spectrum of biological activities, it would be easier to develop new drugs

from saffron after extensive studies on its mechanism of action and pharmacological effects which could be of immense medicinal use in present era.

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