



ORIGINAL ARTICLE

## Chemical and Medicinal Properties of Saffron

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### ABSTRACT

*Crocus sativus L.* belonging to the family Iridaceae comprises the dried red stigma and is widely cultivated in Iran and other countries such as India and Greece. Saffron contains more than 150 volatile and aroma-yielding compounds mainly terpenes, terpene alcohol, and their esters. The bitter taste and an iodoform or hay-like fragrance are caused by chemicals picrocrocin and safranal. *C. sativus* possesses a number of medicinally important activities such as antihypertensive, anticonvulsant, antitussive, antigenotoxic and cytotoxic effects, anxiolytic aphrodisiac, antioxidant, antidepressant, antinociceptive, anti-inflammatory, and relaxant activity. It also improves memory and learning skills, and increases blood flow in retina and choroid. The present review explores the historical background, chemical constituents, pharmacological actions, uses, substitutes and adulterants, and toxicity. It also deals with its evaluation, formulations, and chemical tests in detail.

**Keywords:** Anticonvulsant, antinociceptive, aphrodisiac, crocin, *Crocus sativus*, safranal

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### INTRODUCTION

*Crocus sativus L.* (Iridaceae), commonly known as saffron, is a perennial stemless herb that is widely cultivated in Iran and other countries such as India and Greece. Commercial saffron comprises the dried red stigma with a small portion of the yellowish style attached.(1) The earliest apparent reference to its cultivation goes back to about 2300 BC; Sargon, the founder of the Acedian empire, was born at the otherwise unknown village on the Euphrates called Azupirano - the name meaning perhaps "Saffron town."(2) A definite identification of saffron crocuses dates from about 1700-1600 BC, in the form of a fresco painting in the Palace of Minos at Knossos in Crete. The wild precursor of domesticated saffron crocus was *Crocus cartwrightianus*. Experts believe saffron was first documented in a 7th century BC Assyrian botanical reference compiled under Ashurbanipal. Since then, documentation of saffron's use over the span of 4000 years in the treatment of some 90 illnesses has been uncovered. It is in leaf from October to May, and in flower in October. The flowers are hermaphrodite (have both male and female organs) and are pollinated by bees and butterflies. The plant prefers light (sandy) and medium (loamy) soils, requires well-drained soil, and can grow in nutritionally poor soil. The flower has three stigmas, which are the distal ends of the plant's carpels. Together with the style, the stalk connecting the stigmas to the rest of the plant are often dried and used in cooking as a seasoning and coloring agent. Saffron blooms only once a year and should be collected within a very short duration. It is picked during 3-4 weeks in October-November. The method for the cultivation of saffron contributes greatly to its high price. According to some reports, this species is a sterile triploid and so does not produce fertile seeds. Germination can take 1-6 months at 18°C.(3) It takes 3 years for plants to flower from seed.(4) Saffron is characterized by a bitter taste and an iodoform or hay-like fragrance, which are caused by chemicals picrocrocin and safranal.(5) The value of saffron (stigmas of *C. sativus L.*) is determined by the existence of three main secondary metabolites: crocin, picrocrocin, and safranal.(6) Saffron is used for depression in Persian traditional medicine.(7) Pistils of saffron are generally used in traditional Indian medicine as analgesics and cardio-protective agents, as well as in the treatment of various kinds of mental illnesses. A crude extract of pistils of saffron improves recovery in ischemia/reperfusion injury and learning and memory in rats. In traditional medicines, saffron is recommended as an aphrodisiac agent.(8).

### SCIENTIFIC CLASSIFICATION

Kingdom: Plant

Division: Magnoliophyta  
 Class: Liliopsid  
 Order: Asparagales  
 Family: Iridaceae  
 Genus: *Crocus*  
 Species: *C. sativus*

**SYNONYMS**

Hindi - kesar, zaffran; Sanskrit - avarakta, saurab, mangalya, agnishikha, kumkuma, mangal, kusrunam; English- saffron; Arab and Persian - zafrāh, zipharana; Ben - jafran; Bom - safran, kessar; Mah - kecara; Guj - keshar; Tel - kunkuma-purva, kunkumma-purru; Tam. and Mal. - kunkumappu; Can. and Kon. - kunkuma-kesara; Fr. and Ger. - safran.(3).

**MACROSCOPY**

Color - stigma dark red to reddish brown. Style is yellowish brown to yellowish orange.

Odor - strong, characteristic, and aromatic. Taste - characteristic and bitter. Size- stigmas are 25-mm long, and styles are about 10-mm long. Shape - stigma trifid and styles cylindrical.(9).

**MICROSCOPY**

If the soaked drug is examined under a lens or microscope, the stigmas will be found either separate or united in three to the apex of yellowish styles. Each stigma is about 25-mm long and has the shape of a slender funnel, the rim of which is dentate or fimbriate.(4)

**CHEMICAL CONSTITUENTS**

In view of its wide range of medical uses, the saffron has undergone extensive phytochemical and biochemical studies and variety of biologically active ingredients has been isolated [Tables1], (2). Characteristic components of saffron are crocin-(responsible for the color), picrocrocin- (responsible for the bitter taste), and safranal- (responsible for odor and aroma) [Figure 1].(4) Saffron contains more than 150 volatile and aroma-yielding compounds. It also has many non-volatile active components, many of which are carotenoids including zeaxanthin, lycopene, and various  $\alpha$ - and  $\beta$ -carotenes.(10) The volatiles with a very strong odor are consistent of more than 34 components that are mainly terpenes, terpene alcohols, and their esters. Non-volatiles include crocins 14 that are responsible for the red or reddish brown color of stigmas together with carotenes, crocetin, picrocrocin (a glycosidic precursor of safranal), the bitter substance and safranal the major organoleptic principle of stigmas.(11) However saffron's golden yellow-orange color is primarily due to  $\alpha$ -crocin. This crocin is *trans*-crocetin di-( $\beta$ -D-gentiobiosyl) ester. Systematic (IUPAC) name: 8, 8-diapo-8, 8-carotenoic acid. This means that the crocin underlying saffron's aroma is a digentiobiose ester of the carotenoid crocetin. Crocins themselves are a series of hydrophilic carotenoids that are either monoglycosyl or di-glycosylpolyene esters of crocetin.(10) Meanwhile crocetin is a conjugated polyenedicarboxylic acid that is hydrophobic and thus oil soluble. When crocetin is esterified with two water-soluble gentiobioses (which are sugars), a product results that is itself water soluble. The resultant  $\alpha$ -crocin is a carotenoid pigment that may comprise more than 10% of dry saffron's mass. The two esterified gentiobioses make  $\alpha$ -crocin ideal for coloring waterbased (nonfatty) foods such as rice dishes.(11) A hypothetical protocrocin of the fresh plant is decomposed on drying into one molecule of crocin and two molecules of picrocrocin. Crocin on hydrolysis yields gentiobiose and crocetin, while picrocrocin yields glucose and safranal.(4) The bitter glucoside picrocrocin is responsible for saffron's flavor. Picrocrocin (chemical formula:  $C_{16}H_{26}O_7$ , systematic name: 4-( $\beta$ -d-glucopyranosyloxy)-2, 6,6-trimethylcyclohex-1-ene-1-carboxaldehyde) is a union of an aldehyde subelement known as safranal (systematic name: 2, 6, 6-trimethylcyclohexa-1,3-dien-1-carboxaldehyde) and a carbohydrate. It has insecticidal and pesticidal properties and may comprise up to 4% of dry saffron. Safranal is less bitter than picrocrocin and may comprise up to 70% of dry saffron's volatile fraction in some samples. A second element underlying saffron's aroma is 2-hydroxy-4, 4,6-trimethyl-2,5-cyclohexa-dien-1-one, the scent which has been described as "saffron, dried hay-like." Callus cultures at pH: 7.0-7.6 with added uridine-diphosphoglucose are able to transform all *trans*-crocetin into its related glycosides. An antioxidant 3,8-dihydroxy-1-methylanthroquinone-2-carboxylic, claimed to be superior to vitamin E in its inhibition of oxidation of linoleic acid, has been isolated from callus stem tissue of saffron.(4) Dry saffron is highly sensitive to fluctuating pH levels and rapidly breaks down chemically in the presence of light and oxidizing agent. It must, therefore, be stored in air-tight containers in order to minimize contact with atmospheric oxygen. *C. sativus* has been shown to have anti-depressant effects, two active ingredients are crocin and safranal.(12) As preliminary phytochemical results indicated, it could be suggested that the antinociceptive and anti-inflammatory effects of the petal extracts may be due to their content of flavonoids, tannins, and anthocyanins. Other studies have demonstrated that various flavonoids such as rutin, quercetin, luteolin, hesperidin, and bioflavonoids are present.(13)

| Component                        | Mass percentage |
|----------------------------------|-----------------|
| Carbohydrates                    | 12.0-15.0       |
| H <sub>2</sub> O                 | 19.0-14.0       |
| Polypeptides                     | 11.0-14.0       |
| Cellulose                        | 4.0-7.0         |
| Lipids                           | 3.0-8.0         |
| Minerals                         | 1.0-1.5         |
| Miscellaneous<br>Non-nitrogenous | 40.0            |

Table 1: Chemical composition of saffron

| Component                | Mass percentage |
|--------------------------|-----------------|
| Water soluble components | 53.0            |
| Gums                     | 10.0            |
| Pentosans                | 8.0             |
| Pectins                  | 6.0             |
| Starch                   | 6.0             |
| α- Crocin                | 2.0             |
| Carotenoids              | 1.0             |
| Lipids                   | 12.0            |
| Non volatile oils        | 6.0             |
| Volatile oils            | 1.0             |
| Protein                  | 12.0            |
| Inorganic matter ("ash") | 6.0             |
| HCl soluble ash          | 0.5             |
| Water                    | 10.0            |
| Fiber (crude)            | 5.0             |

Table 2: Proximate analysis of saffron

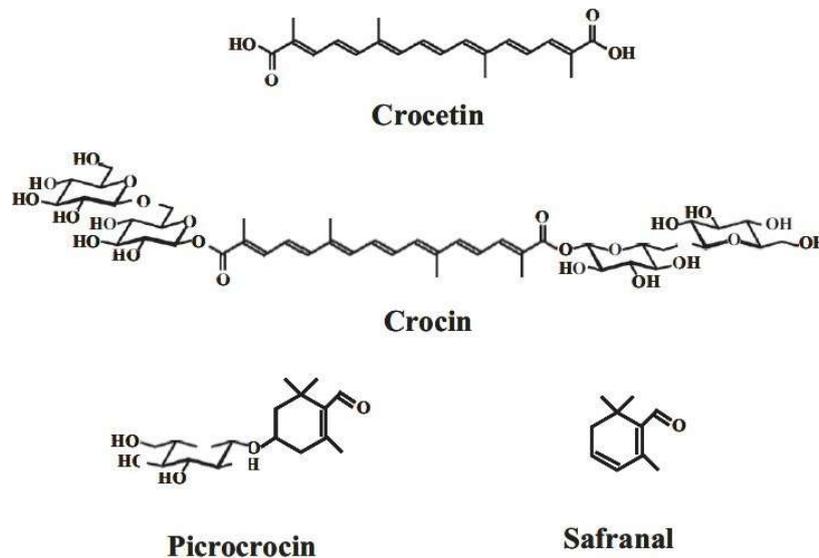


Figure 1: Structures of the chemical constituents

### PHARMACOLOGICAL ACTIONS

Various pharmacological studies have been described that saffron and its constituents exhibit different beneficial properties, including antioxidant, anticancer, anticonvulsant, antiischemic, antigenotoxic,

antidote, antiapoptotic, antitussive, antidepressive, sedative and hypnotic, hypolipidemic, antinociceptive and antiinflammatory effects.(14)

#### **Antihypertensive activity**

Fatehi and others investigated the effects of *C. sativus* petals' extract 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 manner. Administration of 50 mg/g of aqueous extract changed the blood pressure from  $133.5 \pm 3.9$  to  $117 \pm 2.1$  (mmHg). This reduction could either be due to the effect of the *C. sativus* petals' extracts on the heart itself/total peripheral resistance, or both. The effect of extracts on peripheral resistance seems to be more important.(15). In the rat isolated vas deferens, contractile responses to EFS were decreased by the petals' extracts. Contractions of the vas deferens to EFS are mediated by a combination of noradrenaline and ATP released as co transmitters from sympathetic nerves.(16) The ethanol extract induced greater changes in EFS in the rat isolated vas deferens and guinea-pig ileum than the aqueous extract.(15).

#### **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(17).

#### **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.(18)

#### **Antigenotoxic and cytotoxic effects of saffron**

The antimutagenic, comutagenic, and cytotoxic effects were assessed using the Ames/Salmonella test system, two well-known mutagen (BP, 2AA), the *in vitro* colony-forming assay, and four different cultured human normal (CCD-18LU) and malignant cells. When only using the TA98 strain in the Ames/Salmonella test system, saffron showed nonmutagenic, as well as non-antimutagenic activity against BP-induced mutagenicity and demonstrated a dose-dependent co-mutagenic effect on 2-AA-induced antimutagenicity. The saffron component responsible for this unusual co-mutagenic effect was safranal. In the *in vitro* colony-forming 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. Saffron crocin derivatives possessed a stronger inhibitory effect on tumor cell colony formation. Overall, these results suggest that saffron itself, as well as its carotenoid components, might be used as potential cancer chemopreventive agents (19).

#### **Effect on sexual behavior**

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).

#### **Anxiolytic activity**

This study was designed to investigate in rodents whether or not crocins possess 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. (21)

#### **Relaxant property**

To study the mechanism(s) of the relaxant effects of *C. sativus* (Iridaceae), the stimulatory effect of aqueous-ethanolic extracts of this plant and one of its constituent, safranal, was examined on  $\beta$ -adrenoreceptors in tracheal chains of guinea pigs. The  $\beta_2$ -adrenergic stimulatory was tested by performing the cumulative concentration-response curves of isoprenaline-induced relaxation of pre-contracted isolated guinea pig tracheal chains. The studied solutions included two concentrations of aqueous

ethanolic extracts from *C. sativus* (0.1 and 0.2 g%), safranal (1.25 and 2.5 µg), 10 nMpropranolol, and saline. The study was done in two different conditions including non-incubated (group 1,  $n = 9$ ) and incubated tissues with 1 µMchlorpheniramine (group 2,  $n = 6$ ). The results showed clear leftward shifts in isoprenaline curves obtained in the presence of only higher concentration of the extract in group 1 and its both concentrations in group 2 compared with that of saline. The EC<sub>50</sub> (the effective concentration of isoprenaline, causing 50% of maximum response) obtained in the presence of both concentrations of the extract ( $0.17 \pm 0.06$  and  $0.12 \pm 0.02$ ) and safranal ( $0.22 \pm 0.05$  and  $0.22 \pm 0.05$ ) in group 1 and only in the presence of two concentrations of the extract ( $1.16 \pm 0.31$  and  $0.68 \pm 0.21$ ) in group two was significantly lower compared to saline. The maximum responses obtained in the presence of both concentrations of the extract and safranal in group 1 were significantly lower than that of saline. The results indicated a relatively potent stimulatory effect of the extract from *C. sativus* on  $\beta_2$ -adrenoreceptors, which is partially due to its constituent, safranal. A possible inhibitory effect of the plant on histamine (H<sub>1</sub>) receptors was also suggested (22).

#### **Effect on depression**

The efficacy of petal of *C. sativus* was assessed in the treatment of mild-to-moderate depression in a 6-week double-blind, placebo-controlled and randomized trial. Forty adult outpatients who met the Diagnostic and Statistical Manual (DSM) of Mental Disorders, fourth edition for major depression based on the structural clinical interview for DSM IV, participated in the trial. In this double-blind, placebo-controlled and randomized trial, patients were randomly assigned to receive capsule of petal of *C. sativus* 30 mg/day (b.d.) (Group 1) and capsule of placebo (b.d.) (Group 2) for a 6-week study. At 6 weeks, petal of *C. sativus* produced a significantly better outcome on Hamilton Depression Rating Scale than placebo (d.f. = 1,  $F = 16.87$ ,  $P < 0.001$ ). There were no significant differences in the two groups in terms of observed side-effects. The results of this study indicate the efficacy of petal of *C. sativus* in the treatment of mild-to-moderate depression.(23) In further preliminary work, saffron was compared to the drug fluoxetine; it was found that the saffron performed as well as the drug in the treatment of depression.(24) In addition, in a recent pre-clinical study, it has been reported that petal of *C. sativus*, the part of this herb that is very cheap compared to stigma of *C. sativus* (saffron), has antidepressant effect.(25)

#### **Effect on learning behavior and long-term potentiating**

The saffron extract 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.(6)

#### **Effects on ocular blood flow and retinal function**

Crocetin 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.(26)

#### **Effect on coronary artery disease**

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 antioxidant.(27)

#### **Antinociceptive and anti-inflammatory effects**

Saffron stigma and petal extracts exhibited antinociceptive effects in chemically induced pain test as well as acute and/or chronic anti-inflammatory activity, and these effects might be due to the presence of flavonoids, tannins, anthocyanins, alkaloids, and saponins.(7)

#### **Anti Alzheimer's**

The main carotenoid constituent, trans-crocetin-4, the digentibiosylester of crocetin, inhibited A-beta fibrillogenesis formed by oxidation of the amyloid beta-peptide fibrils in Alzheimer's 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 its another constituent dimethylcrocetin.(28)

#### **Hypolipidemic activity**

Crocetin, 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.(29)

#### **Anti pruritic and Emmolient 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.(17)

#### **Antioxidant activity**

The methanolic extract of *Crocus sativus* and its components such as safranal, crocetin etc. were reported to possess radical scavenging activity, suggesting its use as a cosmetic to treat age related disorders, as a food supplement etc.(30)

Crocetin was found to possess greater antioxidant capacity than alpha-tocopherol in neuronally differentiated pheochromocytoma cells deprived of glucose, whose absence caused peroxidation of their cell membrane lipids and decreased intercellular superoxide dismutase activity. These effects were reversed by crocetin, promising it as a unique and potent antioxidant that combats oxidative stress in neurons.(31)

Further it was also said to increase the levels of various enzymes such as the glutathione reductase, glutathione-S-transferase and also maintains the functional levels of other antioxidants suggesting it as a potential antioxidant.

#### **Protection from genotoxicity**

The aqueous extract of saffron prevented the genotoxicity produced by certain drugs such as cisplatin, urethane, cyclophosphamide and mitomycin C in mice bone marrow micronucleus test. Further there was an increase of hepatic enzymes such as the glutathione S-transferase in those animals pretreated with saffron. It was also reported to prevent the oxidative stress induced by these drugs through attenuation of the lipid peroxidation with a simultaneous increase of liver enzymes such as the superoxide dismutase, catalase and non-enzymatic antioxidants suggesting that the chemopreventive effects of saffron are mediated through modulation of lipid peroxidation, antioxidants and detoxification systems.(32)

#### **Cardioprotection**

Crocetin, the main active constituent of saffron was found to decrease the level of cardiac marker - lactate dehydrogenase activity and also increase mitochondrial potential in a cardiac myocyte treated with noradrenaline, suggesting its cardioprotective action.(33)

Saffron was also shown to possess calcium antagonistic activity. This antagonistic activity was through the blockade of extracellular Ca<sup>2+</sup> influx through receptor-operated Ca<sup>2+</sup> channels and potential-dependent Ca<sup>2+</sup> channels.(28)

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.(34)

#### **Anti diabetic activity**

Crocetin, the active constituent of saffron was found to possess antidiabetic 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.(35)

Advanced glycation end products are known to cause the oxidative reaction that usually results in endothelial cell apoptosis and thus result in diabetic vascular complications. Crocetin by virtue of its good antioxidant capacity and calcium antagonistic activity or stabilization may be a good remedy for diabetic vascular complications.(36)

#### **In Respiratory disorders**

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 safranin 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.(37)

#### **Anti Parkinson's activity**

In a model of middle cerebral artery occlusion (model of acute cerebral ischemia) in rats, the decrease in the activity of enzymes such as superoxide dismutase, Na<sup>+</sup>K<sup>+</sup>-ATPase, catalase etc: was countered by pre-treating the animals with crocetin, which suggests the usage of *Crocus sativus* in focal ischemia.(38)

Parkinson's disease, a neurodegenerative disorder is mainly characterized by the degeneration of neurons in the substantia nigra or by injection of certain chemicals like 6-hydroxy dopamine leading to the death of neurons. 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 this devastating disorder.(28)

#### **Effects on uterus**

In traditional medicine, the herb is used for promoting and regulating menstrual periods. It also soothes lower back pains, which accompany menstruation. Saffron is also beneficial in the treatment of other ailments concerning women such as leucorrhoea and hysteria. Preparations of saffron were used in painful conditions of the uterus.(39)

A polyherbal formulation containing saffron when used at the doses of 1000 and 2000 mg/kg was reported to produce contractions of uterus in rats.(40)

#### **Anticancer and antitumour activity**

Ethanol extracts of *Crocus sativus* increased the life span of Swiss albino mice, which were intraperitoneally transplanted with sarcoma-180 cells, Ehrlich as cites carcinoma or Dalton's lymphoma ascites tumours. Saffron in the presence of the T cell mitogen phytohem agglutinin stimulated a non-specific proliferation of T lymphocytes invitro. This suggests that saffron's antitumour activity might be immunologically mediated.(28)

The use of crocetin in lung cancer was found to decrease the lipid peroxidation, glutathione metabolizing enzymes and also revert the histopathological changes relevant to tumour incidence proving it as a potential antitumour agent. Crocetin was found to exert a small inhibitory effect on the development of skin tumours induced in nude mice by the application of 9, 10-dimethyl-1,2-benzanthracene, 7-12 dimethyl benz [ $\alpha$ ] anthracin and croton oil. In rats, crocins revealed a great protective effect against hepatocarcinogenic compounds such as aflatoxin B1 and dimethylnitrosamine, partially suppressing chronic hepatic damage. Crocetin has been found to be a potent inhibitor of skin tumour promotion induced by 12-O-tetradecanoylphorbol-13-acetate in mice.(28)

Topical administration of saffron extracts inhibited the initiation/promotion of 7,12-dimethylbenz [ $\alpha$ ] anthracene-induced skin tumours in mice, delaying the onset of papilloma formation and reducing the mean number of papillomas per mouse. This antitumour effect of saffron was attributed to the increase in the levels of  $\beta$ -carotene and vitamin A in the serum of the experimental animals receiving saffron. The study demonstrated that crocetin had no cytotoxic effect on colony formation of different tumor cells, but had a dose-dependent inhibitory effect on DNA, RNA, and protein synthesis in these human malignant cells. Further a novel glucoconjugate isolated from corms and callus of saffron was showed to possess cytotoxic activity against different tumor cells derived from fibrosarcoma, cervical epithelioid carcinoma, and breast carcinoma. Crocin and diglucosylcrocetin inhibited early tumor antigen expression of adenovirus infected cells crocetin esters were less potent than crocin itself in this concern(28).

#### **Cellular and molecular effects**

It has been demonstrated that crocin possesses antiapoptotic effects on non-cancerous cells. Crocin suppresses cell death induced by tumour necrosis factor-alpha (TNF- $\alpha$ ), cysteine protease mRNAs and simultaneously restores the cytokine-induced reduction of TNF- $\alpha$  and mRNA expression (28).

#### **Crocetin and haemorrhagic shock**

Crocetin, a saffron-derived carotenoid, was shown to improve post shock recovery of cellular adenosine triphosphate and to increase overall survival in an experimental model of hemorrhagic shock. In this model, crocetin caused the suppression and subsequent expression of messenger ribonucleic acid for tumor necrosis factor, interleukin-1 and inducible nitric oxide synthase(42).

## **EVALUATION**

### **Tablet assay**

*C. sativus* stigma tablets were evaluated for short-term safety and tolerability in healthy adult volunteers. The study was a double-blind, placebo-controlled design consisting of a 1-week treatment of saffron tablets. Volunteers were divided into three groups of 10 each (five males and five females). Group 1 received placebo; groups 2 and 3 received 200 and 400 mg saffron tablets, respectively, for 7 days. General measures of health were recorded during the study such as hematological, biochemical, and electrocardiographic parameters done in pre- and post-treatment periods. Clinical examination showed no gross changes in all volunteers after invention. Saffron with higher dose (400 mg) decreased standing systolic blood pressure and mean arterial pressures significantly. Saffron decreased slightly some hematological parameters such as red blood cells, hemoglobin, hematocrit, and platelets. Saffron increased sodium, blood urea nitrogen, and creatinine. This study showed that saffron tablets may change some hematological and biochemical parameters. However these alternations were in normal ranges and they were not important clinically.(43)

### **Quantitative structure-retention relationship**

Quantitative structure-retention relationship (QSRR) studies were performed for predicting the retention times of 43 constituents of saffron aroma, which were analyzed by solid-phase micro-extraction gas chromatography-mass spectrometry (SPME-GC-MS). The chemical descriptors were calculated from the molecular structures of the constituents of saffron aroma alone, and the linear and non-linear QSRR modes were constructed using the best-multi-linear regression (BMLR) and pursuit regression (PPR) methods. The predicted results of the two approaches were in agreement with the experimental data. The coefficients of determination ( $R^2$ ) of the linear BMLR model were 0.9434 and 0.8725 for the training and test sets, respectively. The other non-linear PPR model gave a more accurate prediction with  $R^2$  values of 0.9806 (training set) and 0.9456 (test set). The proposed models could also identify and provide some insights into the structural features that may play a role on the retention behaviors of the constituents of

saffron aroma in the SPME-GC-MS system. This study affords a simple but efficient approach for studying the retention behaviors of other similar plants and herbs.(44)

### Chromatography and spectral analysis

A variety of analytical methods, for example, TLC, HPLC, HPTLC, have been developed for analytical separation and qualitative studies of crocins; quantitative methods for crocins have recently been reported. Methods reported for preparative chromatography of crocins include aluminum oxide column chromatography, (45) TLC, gel column chromatography, and multi-layer coil counter current chromatography, with silica gel, aluminum oxide, Sephadex LH-20 as stationary phases. By use of these methods, the yellow pigments have been separated into seven fractions at most. A preparative HPLC method for saffron has also been reported; [Figures2–5](46) high purity crocins have not, however, been obtained. Eleven certified saffron samples (*C. sativus* L.), one each from Azerbaijan, China, Greece, France, India, Iran, Italy, New Zealand, Spain, Turkey, and the Sigma Chemical Company, were analyzed by using an HPLC photodiode array detection method. This analysis quantified the 10 major saffron compounds in each sample and their concentration was analyzed at three different wavelengths. Result indicated that the Greek Indian, New Zealand, and Spanish saffron extracts possessed the highest concentrations of water-soluble glycosidic carotenoids ( $\geq 8.0\%$ ) suggesting that they could be a good source of this type of metabolite for further biological evaluation.(47)

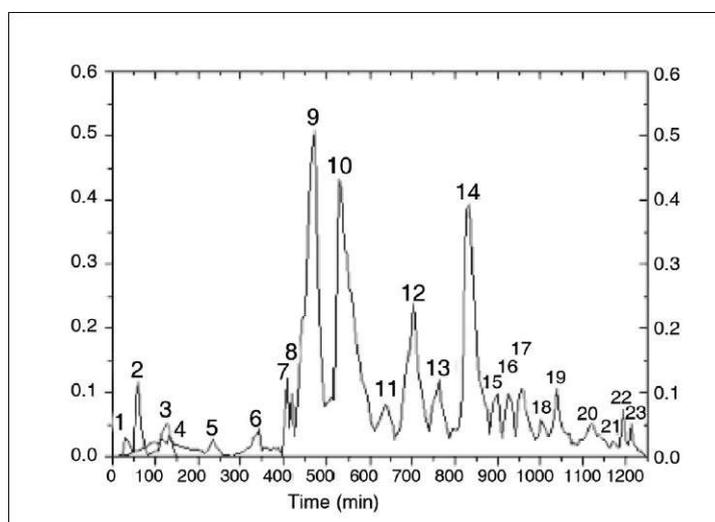


Figure 2: Preparative chromatogram obtained from the saffron extract. For fractions 1 and 2, the detection wavelength was 560 nm. For fraction 3, the detection wavelength was 620 nm. For fractions 4-23, the detection wavelength was 440 nm.

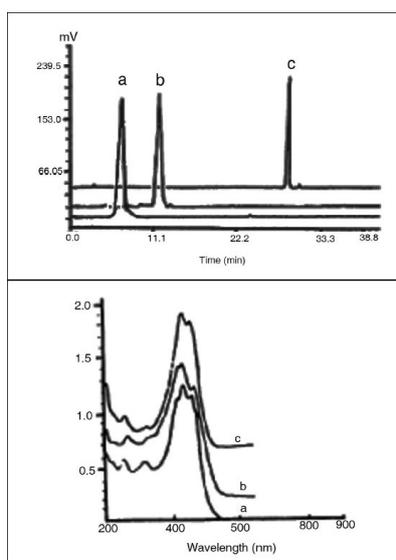


Figure 3: Chromatogram and UV-visible spectra of the crocins: a = crocin 1; b = crocin 2; c = crocin 3.

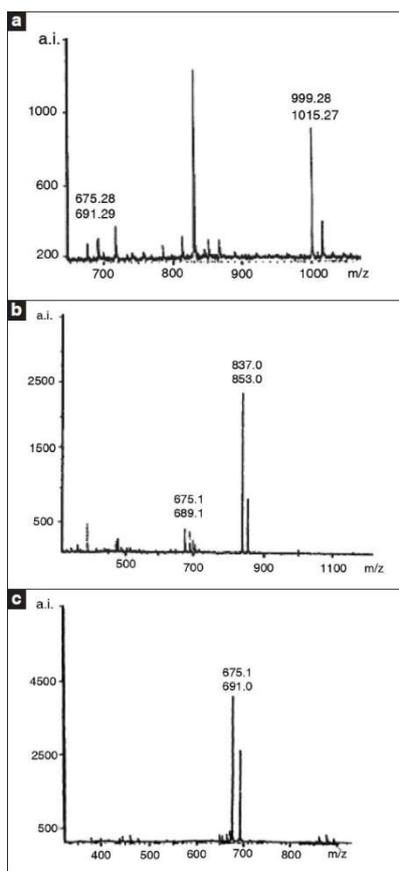


Figure 4: Mass spectra of the crocins: a = crocin 1; b = crocin 2; c = crocin.

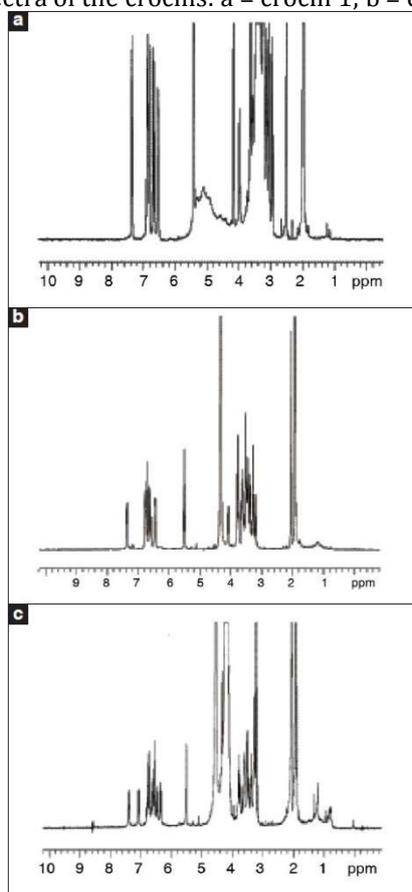


Figure 5: <sup>1</sup>H-NMR spectra of crocin 1 (a), crocin 2 (b), crocin 3 (c).

Thermal desorption-gas chromatography was applied to samples of saffron to quantify the safranal content that is responsible for the distinctive aroma. Safranal constituted 72% of the volatile fraction. Using  $\beta$ -cyclocitral as internal standard and submitting the sample to a temperature of 70°C for 8 min, 83% of the total was determined with the first desorptions, and 100% with three consecutive desorptions.(48)

### TOXICITY STUDIES

Saffron is nontoxic in animal studies (LD<sub>50</sub> - 20.7 g/kg), noncytotoxic in *in-vitro* studies (LD<sub>50</sub> -200 mg/mL). The corms are toxic to young animals. In respect to LD<sub>50</sub> values and maximum non-fatal doses, the stigma extracts were more toxic than the petals' extract and have been reported as 1.6 g/kg, i.p. and 3.38 g/kg, i.p. in mice. According to a toxicity classification, stigma and petals extracts are "relatively toxic" and "low toxic," respectively. Treatment with the *C. sativus* extract also significantly prolonged the life span of cisplatin-treated mice almost threefold.(49) Toxicity studies showed that the hematological and the biochemical parameters were within normal range with saffron extract.(50)

### SUBSTITUTES AND ADULTERANTS

Because of the cost, saffron is frequently adulterated with cheaper substitutes such as marigold flowers and safflower. The flower styles are used as a tea substitute.

The substances used may be grouped in three categories, viz.:(a) substitution of other materials that have some external resemblance to saffron; (b) exhausted saffron recovered by dyes; and (c) substances added to saffron in order to increase its weight.

Materials used as substitutes may be mixed with saffron or supplied in place of saffron, the following have been used: styles of crocus, which are yellowish, slender, and unbranched; stamens and strips of the corolla of saffron crocus; ligulatecorollas of florets of the marigold, *Calendula officinalis*, which are often colored with methyl orange and sometimes known as feminell or Chinese safflower; ligulate florets of safflower, *Carthmustinctorios*. Linn often found in the cake saffron of commerce; slender stems and roots of some monocotyledons (e.g., *Carex*), colored artificially and stigmas of *Zea mays* Linn, known as corn silk.(11)

### FORMULATIONS

1. Itch cream, a topical proprietary polyherbal formulation, is marketed for its antipruritic and emollient properties in xerotic and pruritic skin disorders.  
It contains the following ingredients (v/w basis):  
Extracts of turmeric 16% (*Curcuma longa*), saffron 0.025% (*C. sativus*), sandalwood 8% (*Santalum album*), vetiver 0.5% (*Vetiveriazizanoides*), latakasturi 0.1% (*Abelmoschusmoschatus*), mehendi 3% (*Lawsoniainermis*), tulsi 3% (*Ocimum sanctum*), yashtimadhu 0.5% (*Glycyrrhizaglabra*), turmeric oil 6.1%, surasar 0.5%, and swarnabhasma 0.00032% in a non-greasy cream base q.s.
2. Scar remover skin cream  
Each 100 g contains wheat germ oil (3.50 ml), *Curcuma longa* Linn. (20.0 g), *Azadirachta indica* (2.00 ml), *Santalum album* Linn (1.00 ml), *Citrus sinensis* rind (2.00 g), Rosemary oil (5.00 ml), *Aloe vera* gel (2.00 ml), *C. sativus* (1.00g), cream base q.s. to make (100.00 g).
3. Tincture dose- 5-20 minims
4. Infusion (saffron tea- 1 in 80)  
Dose- 1 to 4 ounce

### USES

#### Saffron in therapeutics

The Ebers papyrus (ca 1550 B.C.) mentions saffron as an ingredient in a cure for kidney problems. (53) It was recommended as an addition to each meal as "a cheering cardiac medicament," but with a warning that excessive quantities acted as an appetite depressant, (54) although a reasonable amount would stimulate appetite and ease headaches and hangovers. In the recent times, it is being used as a remedy for catarrhal infections, for melancholia, to treat liver enlargement, as a nerve sedative, (55) as a carminative, diaphoretic, and emmenagogue. (56) Its extensive use as an abortifacient decreased following reports of fatalities; death has occurred after ingestion of 1.5 g. Saffron has been discovered to be easily the richest known source of riboflavin, with about 100  $\gamma$ /g. (57) Saffron would be likely to offset the decreased diffusivity of oxygen caused by elevated plasma protein and cholesterol level, reduced the severity of atherosclerosis. In addition, serum cholesterol levels were reduced by half. (58) The addition of crocetin to an appropriate nutrient fermentation broth was found to increase the yield of antibiotics and other

products. (59) Modern pharmacological studies have demonstrated that saffron extract or its constituents have antidepressant, (60) anti-inflammatory, anti-tumor effects, radical-scavenging, learning and memory improving properties. (61) Saffron extract also has chemoprotective properties and protects from genotoxin-induced oxidative stress in mice (62). Anticonvulsant effects have been reported in both PTZ and maximal electroshock (MES) models in mice.(63)

#### **Saffron as dye**

Dyes and colored garments (principal pigment of saffron is  $\alpha$ -crocin, a water-soluble carotenoid). Saffron has been used as a histological stain, i.e., as a dye for connective tissue.(64)

#### **Saffron as perfume**

A pleasantly odoriferous compound, safranal,(65) develops during the drying process,(66) probably by enzymatic (65) or thermal dissociation (67) of the bitter compound, picrocrocin.

#### **Saffron in food**

It performs the functions of a spice, adding its faint, delicate aroma, pleasing flavor, and magnificent yellow color to enhance palatability (68).

### **CHEMICAL TESTS**

The U.S.P. provides the following tests for saffron: saffron should not include the yellow styles. When pressed between filtering paper, it should not leave an oily stain. When chewed, it tinges the saliva deep orange-yellow. When soaked in water, it should not deposit any pulverulent, mineral matter, nor show the presence of organic substances differing in shape from that described. On agitating 1 part of saffron with 100,000 parts of water, the liquid should acquire a distinct yellow color. No color is imparted to benzene agitated with saffron (absence of picric acid and some other coal-tar colors). On drying saffron at 100°C (212°F), it should not lose more than 14% of its weight (absence of added water). When thus dried, and ignited with the free access of air, 100 parts of the dry saffron should not leave more than 7.5% ash (absence of foreign inorganic substances) (67).

### **CONTRAINDICATION**

Contraindicated in pregnancy(69).

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