



## MEDICINAL USES AND PHARMACOLOGICAL PROPERTIES OF *CROCUS SATIVUS* LINN (SAFFRON)

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Received: 05 March 2011, Revised and Accepted: 08 April 2011

### ABSTRACT

*Crocus sativus* Linn (Iridaceae) is used widely in tropical and subtropical countries for a variety of purposes in both household and for medicinal purposes. The stigmas of the plant are used for they contain a variety of chemical constituents like the crocetin, crocin and other flavanoids which make them suitable to possess diversified medicinal properties for treating various ailments. In countries like India and other Asian countries, saffron is been used in their traditional medicine from the pre-historic ages. Chemical constituents were studied for their diversified properties and this review focus on the detailed chemical constituents along with the pharmacological properties tested with the plant.

**Keywords:** *crocus sativus*, crocetin.

### INTRODUCTION

*Crocus sativus* Linn (family: Iridaceae) is a flowering plant in the crocus family and is commonly known as saffron. It is widely used as spice and as a coloring and flavoring agent in the preparation of various foods and cosmetics. It is native to Iran and Greece. It is now cultivated largely in Southern Europe, Tibet and other countries. In India, it is mainly cultivated in Kashmir and Uttranchal. The stigmas of the plant are mainly used for therapeutic purposes<sup>1</sup>. The stigmas of *Crocus sativus* Linn. (Saffron) are used as coloring and flavoring agents in the preparation of food in different parts of the world. Apart from its use in preparation of food, the stigmas of the plant are used for the treatment of a variety of disorders traditionally. The medicinal properties attributed to saffron are extensive.

#### Description

*Crocus sativus* Linn is a grass like tuber plant with purple or lilac colored flowers. The flower stalk rises from a bulb, and is a long, white, slender tube; the flower itself being large, and of a beautiful lilac color. Leaves radical, linear, dark green above, pale green below, enclosed in a membranous sheath, sometimes remaining fresh nearly the whole winter. Corolla in two segments, between which the long styles hang out. Stigmas three, large, nearly an inch long, rolled at the edges, bright orange<sup>1</sup>. The stigmas of saffron are the parts that have been used in medicine. They have a pleasantly bitter and somewhat warming taste. They contain a large portion of extractive matter, and a portion of volatile oil. Age and exposure impair them<sup>2</sup>.

#### Medicinal uses

The stigmas of the plant are mainly used for its medicinal properties extensively in traditional medicine for various purposes, as an aphrodisiac, antispasmodic, expectorant, for treatment of stomach ailments, reducing stomachache and for relieving tension. In Persian traditional medicine, it is used for depression. It is also used to treat insomnia and in the treatment of the measles, dysentery, jaundice, cholera etc: Typically it is applied in the form of paste to treat skin diseases like acne. It is also used in weaving industry as a dyeing agent and in the preparation of various perfumes and incense sticks. It is considered as a tonic for heart and nervous system<sup>1</sup> and for smoothing menstruation<sup>2-3</sup>.

Charaka used the powdered stigmas as one of the drugs in the treatment of cataracts, night blindness and poor vision. Sushruta used it as a blood purifier and to treat skin eruptions internally. It is also used as an antibacterial agent, antiseptic, anti-fungal and antiflatulent traditionally<sup>4</sup>.

Saffron was also used as a nervine sedative, emmenagogue, in treatment of fever, melancholia and enlargement of the liver. It is also used as analgesic, diuretic, immune stimulant, interferon inducer, and for inhibiting the thrombin formation. At low doses, it causes the stimulation of the pregnant uterus and in larger amounts it can cause constriction and spasm<sup>5</sup>.

Saffron is also a protective agent against chromosomal damage, a modulator of lipid peroxidation, and an anti seizure, for reducing blood pressure and also used in treatment of psoriasis<sup>6</sup>.

#### Chemical constituents

Chemical studies on *Crocus sativus* stigmas reported that it possesses carotenoids like crocetin (also called  $\alpha$ -crocetin or crocetin-I), its glycosidic forms are digentiobioside (crocin), gentiobioside, glucoside, gentioglucoside and diglucoside.

$\gamma$ -Crocetin (monomethyl ester),  $\gamma$ -crocetin (dimethylester), trans crocetin isomer, 13-cis-crocetin;  $\alpha$ -carotene,  $\beta$ -carotene, lycopene, zeaxanthin and mangicrocin, a xanthone-carotenoid glycosidic conjugate<sup>7</sup>.

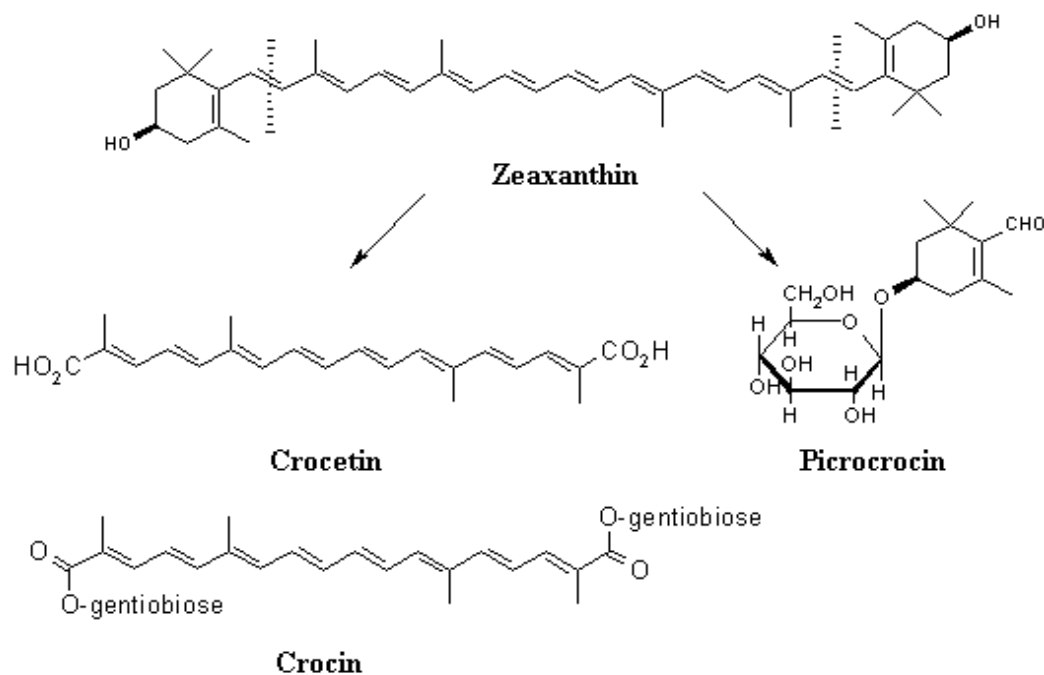
The colouring components of saffron were crocins, which are unusual water-soluble carotenoids (cis and trans glucosyl esters of crocetin). The monoterpene aldehydes picrocrocin and its deglycosylated derivative safranal (dehydro- $\beta$ -cyclocitral), formed in saffron during drying and storage by the hydrolysis of the picrocrocin, are also important components of saffron, responsible of its bitter flavour and aroma, respectively. Saffron's golden yellow orange color is primarily the result of crocin pigments<sup>7</sup>.

Anthocyanins, flavonoids, vitamins (especially riboflavin and thiamine), amino acids, proteins, starch, mineral matter, gums and other chemical compounds presence were also described to make their presence in saffron<sup>6</sup>. Among the constituents of saffron extract, crocetin is mainly responsible for its pharmacological activities<sup>8</sup>.

Other than these Monoterpene aldehydes and isophorone-related compounds like: 2,6,6-trimethyl-4-hydroxy-1-cyclohexen-1-carboxaldehyde, 2,4,4-trimethyl-3-formyl-6-hydroxy-2,5-cyclohexadien-1-one, isophorone, 3,5,5-trimethyl-4-hydroxy-1-cyclohexanon-2-ene, 3,5,5-trimethyl-1,4-cyclohexadione, 3,5,5-trimethyl-1,4-cyclohexadion-2-ene, and 3,5,5-trimethyl-2-hydroxy-1,4-cyclohexadion-2-ene are isolated from the volatile constituents of saffron and studied with IR, UV, NMR and mass spectroscopy<sup>9</sup>.

Apart from these they also contain 5 to 8% fat and wax, 12 to 13 percent protein with a few essential oil that constitutes for the strong smell of saffron<sup>10</sup>.

### Saffron Constituents



### Pharmacological activities

#### A. Anti Alzheimer's:

The main carotenoid constituent, trans-crocetin-4, the digentiobiosyl ester 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 dimethylcrocin<sup>11</sup>.

#### B. Anti tussive activity:

The ethanolic extract of *Crocus sativus* and its constituent safranal, was found to reduce the number of cough in guinea pigs when injected intra peritoneally where a nebulized solution of citric acid (20%) was used to induce cough<sup>12</sup>.

#### C. 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<sup>13</sup>.

#### D. Anti convulsant activity:

Safranal, the coloring agent of saffron, on peripheral administration to rats was found to induce a dose-dependent decrease in the incidence of both minimal clonic seizures and generalized tonic-clonic seizures following pentylenetetrazole administration. This effect of safranal was thought to be mediated at-least in part, through GABA (A)-benzodiazepine receptor complex<sup>14</sup>. Another component of saffron, crocetin did not showed any effect in pentylenetetrazole-induced convulsions in mice<sup>15</sup>.

#### E. 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<sup>16</sup>.

#### F. Anti nociceptive and Anti-inflammatory activity:

The aqueous and ethanolic extracts of saffron stigmas and petals were reported to possess anti nociceptive and anti-inflammatory activity both of, acute and chronic as evidenced by effects in writhing test, xylene induced ear oedema in mice and formalin-induced edema in the rat paw. This supports its traditional use as, an anti-edematogenic remedy<sup>8</sup>.

#### G. 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<sup>17</sup>.

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<sup>18</sup>. 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.

#### H. protection form 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 superoxidisedismutase, catalase and non-enzymatic antioxidants suggesting that the chemopreventive effects of saffron are mediated through modulation of lipid peroxidation, antioxidants and detoxification systems<sup>19</sup>.

### I. Prevention of acetaldehyde-induced inhibition of Long-Term potentiation in rat:

The alcoholic extract of *Crocus sativus* prevented ethanol and acetaldehyde -induced inhibition of hippocampal long-term potentiation in the dentate gyrus of anesthetized rats suggesting its use to prevent aversive effects induced by ethanol and acetaldehyde, its primary metabolite<sup>20</sup>.

### J. Cardioprotection:

Crocetin, the main active constituent of saffron was found to decrease the level of cardiac marker - lactate dehydrogenase activity and also increase mitochondrion potential in a cardiac myocyte treated with noradrenaline, suggesting its cardioprotective action<sup>21</sup>.

Saffron was also showed to possess calcium antagonistic activity. This antagonistic activity was through the blockade of extracellular Ca (2+) influx through receptor-operated Ca (2+) channels and potential-dependent Ca (2+) channels<sup>22</sup>.

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<sup>23</sup>.

### K. 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<sup>24</sup>.

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<sup>25</sup>.

### L. 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 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.<sup>26, 27</sup>.

### M. Effects on ocular blood flow and retinal function:

Crocetin analogs isolated from *Crocus sativus* were found to increase blood flow by vasodilation to the retina and choroid, also facilitate retinal function recovery thereby preventing ischemic retinopathy and age related macular degeneration that results in blindness<sup>28</sup>.

### N. 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+K+-ATPase, catalase etc: was countered by pre-treating the animals with crocetin, which suggests the usage of *Crocus sativus* in focal ischaemia<sup>29</sup>.

Parkinson's disease, a neurodegenerative disorder is mainly characterized by the degeneration of neurons in the substantia nigra by reactive oxygen species 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<sup>30</sup>.

### O. Effect on learning and memory behaviour:

Behavioural and electrophysiological studies have demonstrated that saffron extract affects learning and memory in experimental animals. Aqueous extract of saffron was reported to improve ethanol-induced impairments of learning behavior in mice and ethanol-induced inhibition of hippocampal long-term potentiation, a form of activity-dependent synaptic plasticity that may underlay learning and memory. These effects of saffron extract were attributed to crocin (crocetin di-gentiobiose ester), but not crocetin. Saffron extract or its active constituents, crocetin and crocin, may be useful for the treatment of neurodegenerative disorders accompanying memory impairment<sup>31</sup>. Crocin was also showed to prevent the death of neurons provoked by internal and external apoptotic stimuli by suppressing the TNF- $\alpha$  induced cell death<sup>32</sup>.

### P. Effects on blood pressure:

The aqueous and ethanolic extracts of *Crocus sativus* petals showed a decrease in blood pressure in a dose dependent manner in anaesthetised rats, in isolated rat vas deferens, guinea pig ileum etc. where responses were initiated by electrical stimulation. This decrease in blood pressure was proposed to be mediated postsynaptically<sup>33-34</sup>.

### Q. Antidepressant activity:

*Crocus sativus* petals and hydro alcoholic extracts of the stigmas have shown to possess anti depressant activity in a 6-week double blind, randomized and placebo-controlled trial and in animal based pre-clinical studies. This antidepressant activity was similar to the activity of standard drugs imipramine and fluoxetine<sup>35-37</sup>.

### R. Effects on uterus:

In traditional medicine, the herb is used for promoting and regulating menstrual periods. It also soothes lumber pains, which accompany menstruation. Saffron is also beneficial in the treatment of other ailments concerning women such as leucorrhoea and hysteria. Pessaries of saffron were used in painful conditions of the uterus<sup>38</sup>.

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<sup>39</sup>.

### S. Anticancer and antitumour activity:

Ethanolic extracts of *Crocus sativus* increased the life span of Swiss albino mice, which were intraperitoneally transplanted with sarcoma-180 cells, Ehrlich ascites carcinoma or Dalton's lymphoma sarcoma tumours. Saffron in the presence of the T cell mitogen phytohemagglutinin stimulated a non-specific proliferation of T lymphocytes invitro. This suggests that saffron's antitumour activity might be immunologically mediated<sup>40</sup>.

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<sup>41</sup>.

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<sup>42</sup>. 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<sup>43</sup>.

Topical administration of saffron extracts inhibited the initiation/promotion of 7,12- dimethylbenz [ $\alpha$ ] anthracene-induced skin tumours in mice, delaying the onset of papiloma 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<sup>17</sup>.

Crocetin and diglucoylcrocetin inhibited early tumor antigen expression of adenovirus infected cells crocetin esters were less potent than crocetin itself in this concern<sup>6-7</sup>.

#### T. Cellular and molecular effects:

It has been demonstrated that crocetin possesses antiapoptotic effects on non-cancerous cells. Crocetin 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<sup>6</sup>.

#### U. 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<sup>44</sup>.

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