PHARMACOLOGICAL, PHARMACOGNOSTIC AND PHYTOCHEMICAL REVIEW OF SAFFRON

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Abstract

Since ancient times, herbal plants have been used throughout the world as a source of ayurvedic medicine. Over two millennia ago, the father of medicine Hippocrates mentioned and advised that “let food be your medicine and let medicine be your food”. Currently the morbidity and mortality associated with cancer and depression are considerable and continue to increase. Cancer ranks second and depression stands fourth in mortality. Currently, the above strategies are very attractive and have earned serious consideration as a potential means of controlling these. So many health professionals showed increased interest in these fields and tend to develop a good formulation using an ayurvedic plant as active pharmaceutical ingredient. So, to meet the above needs a bulbous perennial plant called saffron (Crocus sativus .L) was selected and was tend to be used for the treatment of cancer as well as depression. Saffron contains more than 150 volatile and non-volatile components like safranal, crocin, picrocrocin and other carotenoids etc. Saffron is non toxic in animal studies (LD50-20.7g/kg), non-cytotoxic in in-vitro studies (LD50-200mg/kg), and 30mg/day of saffron yields anti–depressant effects. Saffron can be used effectively due to its less toxicity against different human health conditions which allows saffron as a potential medical drug in clinical trails. A vast growing body of research demonstrated that, saffron itself and its main constituents posses chemo preventive and anti-depressant effect. This review discusses recent literature data on different activities of saffron and its main ingredients.
**Introduction:**

Saffron is collected from dried stigmas of bulbous perennial plant called *Crocus sativus* belongs to the family Iridaceae\(^1\). Among the 85 species of *Crocus* genus, saffron is par excellent species due to its medicinal properties and outstanding feature of lilac to mauve colored flower with three stigmas which droop over the petals\(^1\)-\(^2\). The word saffron is derived from the Arabic word Za’faran, which means “yellow” and is named due to its three yellow stamens, which lacks the active components and are not collected. Saffron is cultivated in the Middle Eastern Region of Eurasian continent, from Greece to Persia (Iran)\(^3\). While Iran accounts for 70% of saffron worldwide, kashmiri saffron is widely considered superior due to its higher crocin content (Global press institute). The plant is propagated with the help of corms (bulbs) which divides to produce new plants. Each bulb produces one to seven flowers in which the stigmas are attached to the style\(^4\). The length of the stigmas is of 25-30 mm long. Hybridization of this plant produces an extra long stigmas and takes about 36,000 flowers to yield 1 pound of stigmas. World-wide, 190 tons of saffron are produced each year. Among 150 volatile and non-volatile components of saffron, approximately 40-50 constituents have been already identified and based on these data, we may justify that the pharmacological activity is due to the presence of a carotenoid called crocetin (mono and diglycosyl esters of polyene dicarboxylic acid) and crocin (digentiobiosyl ester of crocetin). The other constituent called picrocrocin is responsible for the bitter taste and volatile oil safranal is responsible for its characteristic honey like flavour\(^5\)-\(^9\). Saffron is non toxic in animal studies (LD\(_{50}\)-20.7g/kg), non-cytotoxic in *in-vitro* studies (LD\(_{50}\)-200mg/kg), and 30mg/day of saffron yields mild to moderate anti–depressant effects and at this dose it has been found to be effective similar to Imipramine\(^10\). It was also found that the side effects like dry mouth and sedation with Imipramine can also be reduced by using saffron as an anti-depressant agent. Along with the above therapeutic effects, saffron has a multifarious applications as a biological specimen. The scientific classification of *Crocus sativus* was given in Table 1.
Table 1: Taxonomical classification of Crocus sativus.

<table>
<thead>
<tr>
<th>Kingdom</th>
<th>Plantae</th>
</tr>
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<tbody>
<tr>
<td>Divison</td>
<td>Magnoliophyta</td>
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<tr>
<td>Class</td>
<td>Liliopsida</td>
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<tr>
<td>Order</td>
<td>Asparagales</td>
</tr>
<tr>
<td>Family</td>
<td>Iridaceae</td>
</tr>
<tr>
<td>Sub-Family</td>
<td>Crocoideae</td>
</tr>
<tr>
<td>Genus</td>
<td>Crocus</td>
</tr>
<tr>
<td>Species</td>
<td>C. sativus</td>
</tr>
</tbody>
</table>

Synonyms

The names of this medicinal plant in 80 languages are mentioned below.

**pharmaceutical Stigmata Croci**

Amharic
Safron
زَعْفَرَان

Arabic
زَعْفَرَان
Zafraan, Zafran

Armenian
Քըրքում, Քրքում

Assamese
Jafaran, Kunkum, Kungkum
Azeri
Zəfəran

Basque
Azaparán, Hupa

Belarusian
Shafran

Bengali
Japhran, Jafran

Bulgarian
Shafran

Catalan
Safrà

Chinese (Cantonese)
番紅花 [fàan húng fāa]

Chinese (Mandarin)
番紅花 [fān hóng huā], 藏紅花 [zàng hóng huā]

Croatian
Vrtni šafran

Czech
Šafrán

Danish
Safran

Dhivehi
Kukun

Dutch
Saffraan
<table>
<thead>
<tr>
<th>Language</th>
<th>Translation</th>
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</thead>
<tbody>
<tr>
<td>Esperanto</td>
<td>Safrano</td>
</tr>
<tr>
<td>Estonian</td>
<td>Krookus, Safrankrookus, Safran</td>
</tr>
<tr>
<td>Farsi</td>
<td>Za'afaran, Zaafaran</td>
</tr>
<tr>
<td>Finnish</td>
<td>Sahrami</td>
</tr>
<tr>
<td>French</td>
<td>Safran</td>
</tr>
<tr>
<td>Gaelic</td>
<td>Crò, Cròdh, Cròch</td>
</tr>
<tr>
<td>Galician</td>
<td>Azafrán</td>
</tr>
<tr>
<td>Georgian</td>
<td>Zaprana, Zaphrana</td>
</tr>
<tr>
<td>German</td>
<td>Safran</td>
</tr>
<tr>
<td>Greek</td>
<td>Κρόκος, Σαφράνι, Ζαφορά</td>
</tr>
<tr>
<td>Greek (Old)</td>
<td>Krokos, Safrani, Zafora</td>
</tr>
<tr>
<td>Gujarati</td>
<td>Kesar</td>
</tr>
<tr>
<td>Hebrew</td>
<td>Safran, Za'afran, Zafran</td>
</tr>
</tbody>
</table>
केसर, ज़ाफ़रान

Hindi
Kesar, Zafran

Hungarian
Füszersáfrány, Sáfrány

Icelandic
Saffran

Indonesian
Kunyit kering, Kuma-kuma, Sapran

Irish
Chróch

Italian
Zaffarano, Zafferano

Japanese
さフラン, バンコウカ

Kannada
Agnishikhe, Kunkuma kesari, Kesari

Kashmiri
Kung, Zafaran

Kazakh
Jawqazin, Zağıparan, Zapırangül

Khmer
Romiet

Korean
사프란, 샤프란
<table>
<thead>
<tr>
<th>Language</th>
<th>Name</th>
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<tbody>
<tr>
<td>Latin</td>
<td>Crocus, Safranum</td>
</tr>
<tr>
<td>Latvian</td>
<td>Safrāna krokuuss, Safrānaugs</td>
</tr>
<tr>
<td>Lithuanian</td>
<td>Šafrenas</td>
</tr>
<tr>
<td>Macedonian</td>
<td>Šafran</td>
</tr>
<tr>
<td>Malay</td>
<td>Koma koma</td>
</tr>
<tr>
<td>Malayalam</td>
<td>Kashmeeran, Kungumampoovu, Kunkumapu</td>
</tr>
<tr>
<td>Maltese</td>
<td>Žaghfran, Žafran</td>
</tr>
<tr>
<td>Marathi</td>
<td>Keshar</td>
</tr>
<tr>
<td>Nepali</td>
<td>Kesar, Kung-kum</td>
</tr>
<tr>
<td>(Nepalbhasa)</td>
<td>Kesar</td>
</tr>
<tr>
<td>Norwegian</td>
<td>Safran</td>
</tr>
<tr>
<td>Oriya</td>
<td>Kesara, Kunkuma phul</td>
</tr>
<tr>
<td>Pahlavi</td>
<td>Kurkum</td>
</tr>
<tr>
<td>Pashto</td>
<td>Zaffaron</td>
</tr>
</tbody>
</table>
Polish  Krokus uprawny, Szafran
Portuguese  Açafrao, Açaflor
Provençal  Safran
Punjabi  चेमठ, चेमठ
Punjabi  Keshar, Kesar
Romanian  ofran (Șofran)
Russian  Шафран
Sanskrit  Kumkuma, Kashmiirajan, Kashmiiran, Nagakeshara
Serbian  Šafran
Slovak  Šafrán siaty, Šafrán
Slovenian  Žafran
Spanish  Azafrán
Swahili  Zafarani
Swedish  Saffran
Tagalog  Kashubha
Tamil  கஞ்சுபாம்
Telugu  కంగుమపుయు
Kunkumapuvvu

Thai

Ya faran

Tibetan

Gur-kum, Kha-che kye, Kunkum (uncertain)

Turkish

Safran, Zağferan

Ukrainian

Shafran, Krokus

Urdu

Zafran, Kisar

Uzbek

Зафарон

Vietnamese

Màu vàng nghe, Quí nghe, Nghể tày

Yiddish

Zafren, Zafron
Origin and cultivation\textsuperscript{11,14}

Saffron was cultivated from back more than 3000 years. It was originated from a wild precursor named \textit{Crocus cartwrightianus}. Experts believe that saffron was first documented in 7\textsuperscript{th} century BC. Mild winters with heavy snowfall and hot summers are excellent conditions for the plant’s growth. Saffron grows well under temperate and dry climates; its vegetative growth coincides with cold weather and freezing condition. Annual rainfall requirement for saffron is about 300 mm. Saffron’s maximum water requirement is in March and April of about 15 to 20 liters per m\textsuperscript{2} per irrigation period. Saffron tolerates maximum of +45°C and minimum of -18°C. Planting is mostly done in June and corms are lodged 7-15 cm deep. Mother corms are planted deeper that yields high quality saffron but yields less flowers. \textit{Crocus sativus} prefers loose, low density, well-watered and well-dried calcareous soils with high organic solvent. After a period of dormancy through the summer, harvesting is done at the time when flowers quickly wilt as the day passes. Few images of this plant are shown in Fig 1,2,3.

![Fig-1 (Flower with stigmas)](image1)
![Fig-2 (corms)](image2)
![Fig-3 (Dried stigmas)](image3)

Phytochemical constituents\textsuperscript{15-18}

Saffron consists of a wide range of chemical constituents as shown in the Table 2.

The other active components are essential oils (volatile oil) in 0.3-1.5\%, crocin derived from crocetin about 2\%, carotenes 8\%, picrocrocin and safranal 4\%. The active constituents present are the degradative products of
zeaxanthin and to a small extent from lycopene and beta-carotene. The degradative products from zeaxanthin formed from bio-oxidative cleavage are shown in the graphical abstract below.

**Table 2: Chemical Constituents of *crocus sativus***.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple sugars</td>
<td>12–15%</td>
</tr>
<tr>
<td>Water</td>
<td>9–14%</td>
</tr>
<tr>
<td>Proteins, amino acids, other nitrogen compounds</td>
<td>11–13%</td>
</tr>
<tr>
<td>Cellulose (fiber)</td>
<td>4–7%</td>
</tr>
<tr>
<td>Fats</td>
<td>3–8%</td>
</tr>
<tr>
<td>Minerals (measured as acid soluble ash)</td>
<td>1–1.5%</td>
</tr>
<tr>
<td>Other non-nitrogen (mainly complex sugars)</td>
<td>about 40%</td>
</tr>
</tbody>
</table>
Toxicity: No toxic effect was seen on human body with saffron consumption. But excess consumption leads to narcotic effects in the body.

Alzheimer’s disease: Saffron at the dose of 30 mg/day (15 mg twice per day) or donepezil 10 mg/day (5 mg twice per day) was found to be effective similar to donepezil in the treatment of mild-to-moderate alzheimer’s disease after 22 weeks.

Anti-depressant effect: Antidepressants activity is due to increment in brain serotonin, norepinephrine and dopamine concentration. Some investigators have proposed that the extract may induce its anti-depressant activity via interaction with serotonin. 30mg/day of saffron yields mild to moderate anti-depressant effects and at this dose it has been found to
be effective similar to Imipramine. It was also found that the side effects like dry mouth and sedation with Imipramine can also be reduced by using saffron as an anti-depressant agent.

**Anti-oxidant effect**\(^{24,25}\)

It was shown that, antioxidant activity of saffron carotenoids is more effective than safranal. However, the synergistic effect of all the bioactive constituents gives to saffron spice a significant antioxidant activity. The antioxidant activity of saffron compounds can protect DNA and tRNA from harmful chemical reactions in these ligand–polynucleotide complexes but in order to have a solid proof for that, further experimental work has to be performed in order to prove that the oxidation products of the saffron compounds does not harm DNA/tRNA.

**Anti-inflammatory effect**\(^{26,27}\)

Microglial cells play critical roles in the immune and inflammatory responses of the central nervous system (CNS). Crocin or crocetin represses microglial activation. Crocin and crocetin were shown to be effective in the inhibition of LPS-induced nitric oxide (NO) released from cultured rat brain microglial cells. These compounds reduced the LPS-stimulated productions of tumor necrosis factor-\(\alpha\), interleukin-1\(\beta\), and intracellular reactive oxygen species. These compounds also effectively reduced LPS-elicited NF-\(\kappa\)B activation. In addition, Crocin reduced NO release from microglia stimulated with interferon-\(\gamma\) and amyloid-\(\beta\). In organotypic hippocampal slice cultures, both crocin and crocetin blocked the effect of LPS on hippocampal cell death. These results suggest that crocin and crocetin provide neuroprotection by reducing the production of various neurotoxic molecules from activated microglia.

**Bactericidal effect**\(^{28-30}\)

Safranal and crocin, the main compounds responsible for the flavouring and colouring are capable of exhibiting bactericidal effect in the order of 8-16 mg/mL and 64-128 mg/mL for safranal and crocin, respectively. These data suggest that these compounds, and probably their chemical relatives, are involved in the antibacterial activity of saffron, and that this effect can significantly reduce the risk of food contamination with Salmonella by this spice.
Effect on coronary artery disease

Fifty milligrams of saffron dissolved in 100 ml of milk was administered twice a day to human subjects as reported in an Indian study published in 1998. The significant decrease in lipoprotein oxidation susceptibility in patients with coronary artery disease (CAD) indicates the potential of saffron as an antioxidant.

Effect on learning behavior and long-term potentiation

Several Japanese studies have reported that 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. These results suggest that oral administration of saffron may be useful as treatment for neurodegenerative disorders and related memory impairment. Recently, it was shown that crocin isolated from saffron exhibits anti-apoptotic action in PC-12 cells treated with daunorubicin. These findings suggest that crocin inhibits neuronal death induced by both internal and an external apoptotic stimulus in highly differentiated cells (neurons). This selective behavior suggests important therapeutic implications, related to the fact that programmed cell death is reduced in cancer and increased in neurodegenerative disease.

Anti cancer activity

Different hypotheses for the modes of anticarcinogenic and antitumor actions of saffron and its components have been proposed. One of the mechanisms for the antitumor or anticarcinogenic action of saffron and its components is the inhibitory effect on cellular DNA and RNA synthesis, but not on protein synthesis. A second suggested mechanism for the antitumor action of saffron and its constituents is the inhibitory effect on free radical chain reactions, because most carotenoids are lipid-soluble and might act as membrane-associated high-efficiency free-radical scavengers, which is connected with their antioxidant properties. A third proposed mechanism by which the saffron extract exerts its antitumor effect is the metabolic conversion of naturally occurring carotenoids to retinoids, but recently, it was reported that conversion carotenoids to vitamin A is not a prerequisite for anticancer activity. A fourth suggested mechanism is that the cytotoxic effect of saffron is connected with interaction of carotenoids with topoisomerase II, an enzyme involved in cellular DNA-
protein interaction. Recently, several other mechanisms for the antitumor effect of saffron and its constituents have also been proposed. It was demonstrated that a novel glucoconjugate, isolated from corm and callus extract of saffron, caused swelling and local plasma membrane evagination, and it was suggested that cytotoxicity is mediated via extracellular fluid uptake. It was also reported that saffron contains lectins, and it might also be suggested that antitumor activity of saffron is mediated via lectins. Treatment of tumor cells with saffron resulted in an increase in the level of intracellular sulphydryl compounds, and this could be one explanation for the potentiation of saffron cytotoxicity. Another suggested mechanism is that cytotoxic effect of carotenoids from saffron is mediated via apoptosis. Interesting studies indicate that encapsulation in amorphous polymer matrices of saffron extracts or saffron carotenoids greatly improves their stabilities and enhances their antitumor effects. More recently, it was shown that γ-irradiation, necessary for microbial decontamination, did not produce significant qualitative changes of volatile essential oil constituents of saffron, but induced a slight decrease in glycosides and an increase in aglycone content in carotene constituents of saffron. This relative stability of saffron to irradiation should also be taken to account in the search for an explanation of the chemopreventive potential of this spice. Thus, although several hypotheses have been put forward, the exact mechanism(s) of anticarcinogenic and antitumor effects of saffron and its main constituents are not clear at present.

**Anticonvulsant effect**

In Iranian traditional medicine, saffron had been used as an anticonvulsant remedy. Recently, in experiments with mice using maximal electroshock seizure (MES) and pentylenetetrazole (PTZ) tests, Iranian scientists have demonstrated that the aqueous and ethanolic extracts of saffron possess anticonvulsant activity. These authors suggested that saffron extracts might be beneficial in both absence and tonic clonic seizures.

**Ophthalmic**

*In vitro* experiments demonstrated a concentration-dependent protective effect of the carotenoid, crocin and its analogs on animal retina. Increased blood flow in the retina and choroid has been demonstrated. As a dietary
supplement, saffron extract prevented retinal damage in rats, and it may have a role in the treatment of ischemic retinopathy and age-related macular degeneration.

**Other uses**

Saffron is also used for treating various skin ailments, skin fairness, indigestion, diarrhea, nausea, vomiting, body pains, nerve weakness, dysurea, impotency, erectile dysfunction, menstrual disturbances, fever, psoriasis\(^5\) etc.

**Conclusion:**

Nature has gifted our planet earth with millions of species of the plants which are scientifically important. One among them being *Crocus sativus*. This plant is a boon to the human society. Therefore, the herbs are to be used for the treatment of any diseases and proper researches has to be carried out to prove it less harmful than the allopathic medicines. In this review, we have tried to present the important and the most recent findings on the uses of the plant, *Crocus sativus*.

**References**


13. Teale; Stephen A.; Webster; Francis X.; Zhang; Aijun, New aggregation pheromone for the bark beetle Ips pini and uses thereof , United States Patent 5,167,955, December 1, 1992


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