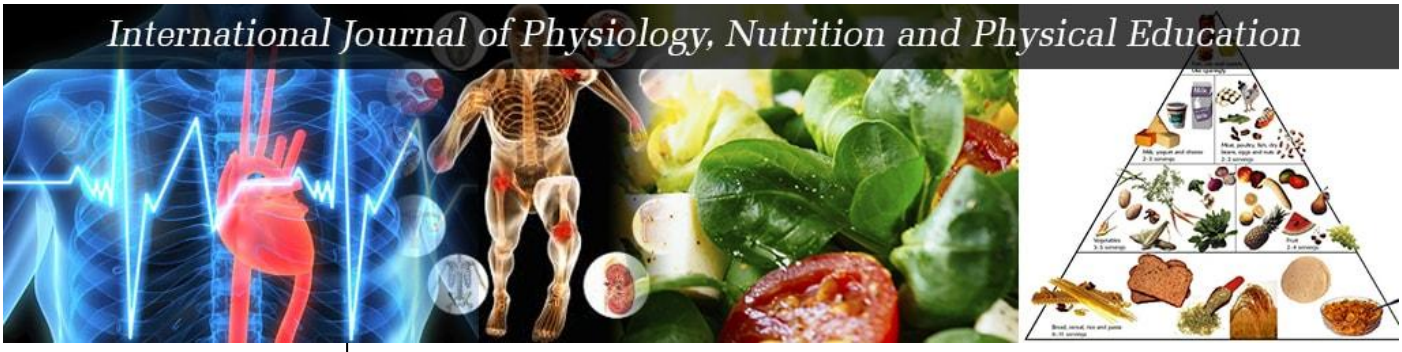

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Pharmacological effects of crocus sativus (zaffran) and its chemical constituents: A review

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Abstract
Crocus sativus (Zaffran) belongs to the family of Iridaceae comprises the dried red stigma. It 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 is caused by chemicals picrocrocin and safranal. Zaffran possesses a number of medicinally important activities such as aphrodisiac, cardioprotective effect**,** antihypertensive, anticonvulsant, antitussive, anti-inflammatory and analgesic effects, antidiabetic effects, antigenototoxic and antioxidant, antidepressant, and antinociceptive activity. It also improves memory and learning skills, and increases blood flow in retina and choroid. The present review explores the chemical constituents, pharmacological activity.

Keywords: Crocus sativus, zaffran, saffron, crocin, safranal, picrocrocin

Introduction
Crocus sativus (Iridaceae) commonly known as Saffron or Zaffran is a perennial bulbous herb. Saffron has long been used as both spice and medicine by a number of cultures. It was mentioned that saffron stigma was used as a medicine over 3,600 years ago [1]. The plant has been priced since antiquity for its yellow-orange coloured tripartite stigmas that constitute the Saffron. Also known as saffron crocus, the odour of saffron is described as like the "sea" air. Crocus is an important genus consisting of 80 species [2]. Some species of Crocus have been cultivated worldwide for use in folk medicines and for colouring purposes. C. sativus L. is principally grown in Spain, India, Turkey, Greece, Austria, Belgium, France, Germany, Holland, Hungary, Italy, Japan, Norway, Russia, Switzerland, Turkey, Persia and the People's Republic of China [3-5].

Taxonomical classification
Kingdom: Plantae
Division: Magnoliophyta
Class: Liliopsida
Order: Asparagales
Family: Iridaceae
Genus: Crocus
Species: C. sativus [6].

Chemical constituents
Saffron has undergone extensive phytochemical and biochemical studies and variety of biologically active ingredients has been isolated. Characteristic components of saffron are crocin-(responsible for the color), picrocrocin- (responsible for the bitter taste), and safranal-(responsible for odor and aroma) [7]. 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 α- and β-carotenes [8]. 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 [9]. However saffron's golden yellow-orange color is primarily due to α-crocin.

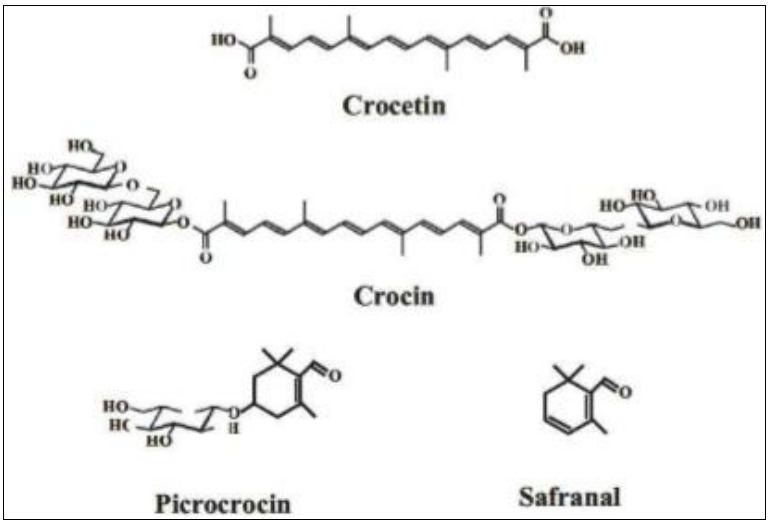

Fig 1: Phytochemical constituents

This crocin is trans-crocetin di-(β-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 [8]. 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 α-crocin is a carotenoid pigment that may comprise more than 10% of dry saffron's mass. The two esterified gentiobioses make α-crocin ideal for coloring waterbased (non-fatty) foods such as rice dishes [9]. 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 [7]. The bitter glucoside picrocrocin is responsible for saffron's flavor. Picrocrocin (chemical formula: C16H26O7, systematic name: 4-(β-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 upto 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 ρH: 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 [7]. 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 [10]. 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 [11].

Pharmacological activities

Aphrodisiac activity

An aphrodisiac is a substance that stimulates the sexual activity or sexual desire in human/animals, either by phychophysiological or internal. The aqueous extract of saffron stigmas containing the compounds safranal and crocin was evaluated on male rats to check aphrodisiac activity. The result proved that the extract containing crocin had aphrodisiac properties [12].

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 [13].

Cardioprotective effect

Cardioprotective activity is shown by certain class of drugs as angiotensin-converting enzyme inhibitor that reduces peripheral arterial resistance by converting angiotensin I to the vasoconstrictor angiotensin II which activates the enzyme, used in treatment of hypertension, congestive heart failure and other cardiovascular disorders. S.N. Goyal *et al*., investigated the isoproterenol (ISO)-induced cardiotoxicity with reference to hemodynamic, antioxidant, histopathological and

ultrastructural parameters with the effect of crocin, the active constituent of saffron. The result proved that crocin had the ability to protect the cardiotoxicity which maintains in the redox status through the modulation of oxidative stress in the cell [14].

Antioxidant activity

Antioxidant is a substance which reduces destruction because of oxygen that caused by free radicals. It includes beta carotene, vitamin E and vitamin C, which could be able to concentrate the harmful effects of oxidation. An investigation was done on in-vitro antioxidant activity and toxicological effects of Crocus sativus L. and it has been concluded that the extract was non-toxic and did not cause any moralities in mice after oral administration [15].

Total antioxidant capacity of human plasma has been examined by a simple, fast and economical crocin assay using Crocus sativus L. and that has been compared with the standard 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. They found that both assays are matching well and showed better sensitivity for natural compounds [16]. Another study by C.D. Kanakis *et al*. evaluated, at the physiological conditions the antioxidant activities of some compounds of saffron and the spectroscopic results have been compared. They found that all the compounds of saffron have the antioxidant activity; especially the carotenoid has the most effective antioxidant activity. The harmful chemical reaction of DNA and tRNA also been protected by the saffron compounds in the ligand polyneucleotide complexes [17].

The saffron compounds such as crocin, kaempferol and podophyllotoxin has been checked for an antioxidant activity by chemical, biochemical and electrochemical assays. It was found that the electrochemical assay showed scavenging ability on superoxide anion which was due to reduction of oxygen that provides better antioxidant potential. The crocin has the highest radical scavenging property mainly due to the hydroxyl and glucose moieties [18].

Anticonvulsant activity

The anticonvulsant activity of the aqueous (0.08-0.8 g/kg) and ethanolic extracts (20-40 mg/kg) of Crocus sativus stigma (CSS) was studied in mice using pentylenetetrazole (PTZ) and the maximal electroshock seizure (MES) tests. In the PTZ test, CSS delayed the onset of tonic convulsions, but failed to produce complete protection against mortality. In the MES test, both extracts decreased the duration of tonic seizures [19].The anticonvulsant activities of Crocus sativus stigma constituents, safranal and crocin, were studied using pentylenetetrazole (PTZ)-induced convulsions in mice. Safranal (0.15 and 0.35 mg/kg body weight, ip) reduced the seizure duration, delayed the onset of tonic convulsions, and protected mice from death. Crocin (22 mg/kg, ip) did not show anticonvulsant activity [20]. Safranal is an effective anticonvulsant, it was an agonist at GABAA receptors, and the nose to brain delivery via nanoparticle formulation improved its brain delivery [21].

Anti-inflammatory and analgesic effects

The preventive effect of the aqueous extract of saffron was studied against diazinon (DZN) -induced rise of several specific inflammation, oxidative stress and neuronal damage in rats. Vitamin E (200 IU/kg) and the aqueous extract of saffron at doses 50, 100 and 200 mg/kg were injected intraperitoneally three times per week alone or with DZN (20 mg/kg/day, orally) for 4 weeks. Red blood cell (RBC) cholinesterase activity was inhibited by DZN and this effect was not affected by vitamin E or saffron plus DZN. The levels of serum tumor necrosis factor-α (inflammation marker), direct 8-iso-prostaglandin F2α (oxidative stress marker) and soluble protein-100 β (S100β, neuronal damage marker) were increased significantly by DZN. The saffron extract inhibited the effect of DZN on these biomarkers levels. However, vitamin E was able to only reduce 8iso-prostaglandin F2α and S100β levels [22]. The antinociceptive and anti-inflammatory activity of saffron extracts were evaluated in mice using aqueous and ethanolic maceration extracts of Crocus sativus stigma and petals. Antinociceptive activity was examined using the hot plate and writhing tests. 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. Naloxone partially blocked only the antinociceptive activity of the stigma aqueous extract. 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 effects [23].

Antidiabetic effects

The ameliorative effect of saffron aqueous extract on hyperglycemia and oxidative stress on diabetic encephalopathy was studied in streptozotocin induced diabetes mellitus in rats. Saffron at 40 and 80 mg/kg significantly increased body weight and serum TNF-α and decreased blood glucose levels, glycosylated serum proteins, and serum advanced glycation endproducts (AGEs) levels which triggered oxidative reaction [130]. Advanced glycation end products (AGEs) were causally correlated with diabetic vascular complications. AGEs triggered oxidative reaction then accelerated endothelial cell apoptosis which was a critical event in the process of vascular complications. Exposure of bovine endothelial cells (BEC) to 200 g/ml AGEs for 48h resulted in a significant increase in apoptotic rate, compared with control. Crocetin (a metabolite of crocin) prevented AGEs-induced BEC apoptosis, which correlates with crocetin attenuation of AGEs mediated increase of intracellular reactive oxygen species (ROS) formation and elevation of intracellular Ca2+ concentration ([Ca2+]i) level ($P < 0.01$ versus AGEs group). These results demonstrate that crocetin prevents AGEs-induced BEC apoptosis through ROS inhibition and ([Ca2+]i) stabilization and suggest that crocetin exerted a beneficial effect in preventing diabetes-associated vascular complications [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 [25].

Antinociceptive activity

The effects of aqueous and ethanolic maceration extract of Crocus sativus L. stigmas (CSS) and petals were studied in mice. The antinociceptive effects of the extracts may be due

to their content of flavonoids, tannins, anthocyanins, alkaloids and saponins. Antinociceptive activity was examined using the hot plate and writhing tests. In hot plate test, aqueous and ethanolic petal extracts showed no significant antinociceptive activity but it exhibit antinociceptive activity against acetic acid induced writhing. It is concluded that saffron stigma and petal aqueous and ethanolic maceration extracts shows antinociceptive effects in chemical pain tests [26-27].

Cellular and molecular effects

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

Hypolipidemic 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 malabsorbtion of fat andcholesterol producing hypolipidemic effect [29].

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 ± 3.9 to 117 ± 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 [30]. 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 cotransmitters from sympathetic nerves [31].The ethanol extract induced greater changes in EFS in the rat isolated vas deferens and guinea-pig ileum than the aqueous extract [32].

Antigenototoxic and cytotoxic effects

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 (Hela, a-204 and Hepg2) 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 [33].

Antianxiety activity

The anxiolytic and hypnotic effects of saffron aqueous extract and its constituents, crocin and safranal were studied in mice. Agents were administered intraperitoneally in mice before the experiments for the evaluation of hypnotic activity (induced by sodium pentobarbital, 30 mg/kg, ip), anxiolytic activity (elevated plus maze test), locomotor activity (open field test) and motor coordination (Rotarod test). The aqueous extract reduced the locomotor activity dose dependently. At low doses, saffron showed a significant increase in the time on the open arms of the maze. When using the Rotarod method, the aqueous extract showed considerable effect on motor coordination of the mice. In the hypnotic test, only a dose of 0.56 g/kg of saffron increased the total sleep. Crocin showed no anxiolytic, hypnotic or myorelaxation effects. Safranal, in higher doses, 0.15 and 0.35 ml/kg, showed anxiolytic effects. Safranal increased the total sleep time dose dependently. This constituent at lower doses (0.05 and 0.15 ml/kg) decreased some locomotion activity parameters. Safranal demonstrated no effects on motor coordination. Based on the results, saffron aqueous extract and safranal showed anxiolytic and hypnotic effects [34]. Intragastric administration of 125–250 mg/kg bw of a 50% ethanol extract of the stigmas showed tranquillizing effect and potentiated the sedative effects of barbiturates in mice [35]. The anxiolytic properties of crocins were investgated in rodents via light/dark test. Crocins, at a dose which did not influence animals' motor activity (50 mg/kg), or diazepam (1.5 mg/kg), increased the rats latency to enter the dark compartment and prolonged the time spent in the lit chamber. Lower doses of crocin (15-30 mg/kg) did not modify animals' behavior [36].

Conclusions

Saffron or Zaffran has been widely used as a medicinal plant to promote human health. The main components of saffron are crocin, picrocrocin and safranal. Saffron has been suggested to be effective in the treatment of a wide range of disorders including aphrodisiac, cardioprotective effect, antihypertensive, anticonvulsant, antitussive, anti-inflammatory and analgesic effects, antidiabetic effects, antigenototoxic and antioxidant, antidepressant, and antinociceptive activity. This review was designed to highlight the chemical constituents and pharmacological effects of Crocus sativus.

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