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Stigma Croci: An Overview

Khaled Mohamed Mohamed Koriem [1,*]

[1] Department of Medical Physiology, Medical Research and Clinical Studies Institute, National Research Centre, 33 El-Buhouth Street, Dokki, Cairo, 12622, Egypt
* Correspondence: kkoriem@yahoo.com (K.M.M.K.);

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Abstract: Stigma Croci refers to *Crocus sativus* L. dry stigma. This plant belongs to the Iridaceae family. The plant is spreading widely in southern Europe, southwestern Asia, and the Eastern Mediterranean region. Stigma Croci is known as *Crocus hispanicus*, *Crocus orientalis*, Crocus, and dye saffron. The powdered Stigma Croci is orange or red in color. The dried Stigma Croci odor is characteristic and aromatic. The major constituents of Stigma Croci are picrocrocin, safranal, and crocins. Stigma Croci is used as a tonic, antiarteriosclerotic, and relaxing factor. Stigma Croci has been used for centuries to stimulate the female menstrual cycle and treat menstrual cycle stop, coughs, digestive ailments, abdominal pain, fever, depression, and pain associated with wounds. Stigma Croci is used in folklore medicine as an aphrodisiac, contraceptive, diaphoretic, appetite stimulant, and nerve relaxing agent. Pharmacology of Stigma Croci includes experimental pharmacology and clinical pharmacology. Experimental pharmacology includes antiarteriosclerotic, anticoagulant, cell proliferation inhibition, central nervous system, chemical carcinogenesis inhibition, circulation, anti-inflammatory, nootropic, and cytotoxicity activities. The lethal dose of fifty of Stigma Croci is equal to 20.7 g/kg bw in rats while the LD_{50} of ethanol extract of Stigma Croci = > 600 mg/kg bw in mice. The extracts of Stigma Croci were not mutagenic. Platelet accumulation is inhibited by Stigma Croci. The intake of dimethylcrocetin constituent of Stigma Croci in animals did not exhibit hematological or biochemical toxic effects after intra-gastric injection up to 50 mg/kg bw. Stigma Croci is occurred in 2 forms (the dried stigmas and extracts). No risk is associated with consumption of Stigma Croci in a standard food and the recommended therapeutic daily dose of Stigma Croci = 3-9g.

Keywords: Stigma Croci; *Crocus sativus* L.; Iridaceae; pharmacology; toxicology; dose.

1. Introduction

Stigma Croci refers to *Crocus sativus* L. (Iridaceae) dry stigma [1,2]. Stigma Croci is known as *Crocus officinalis* Martyn [3]. Other names of Stigma Croci include *Crocus hispanicus*, *Accfrao*, *Crocus orientalis*, *Azaferan*, *Azafran*, and *Crocus* [1-5]. The geographical distribution of *Crocus sativus* L. plant is in the south of Asia and Europe. *Crocus sativus* L. plant is also found in the Mediterranean area, and it is distributed in Italy, France, Spain, China, and India [4,5]. Description of *Crocus sativus* L. plant is as follows: *Crocus sativus* L. plant is a perennial, small shrub (8-30 cm high), an herb with a round rhizome. The plant has 6-9 sessile leaves, surrounded by 4 or 5 broad membranous scales. The plant flowers have occurred at the end of each stem branch; each flower is a pale reddish/purple perianth (10 cm long and 6 elongated rectangle parts). The plant ovary is inferior with 3-locular. The plant style is lean, long, and yellow, and the plant separates into 3 floppy and red stigmas [4,6]. Stigma Croci is

occurred in 2 forms (the dried stigmas and extracts). The stigmas are thin stigmas. Its color ranges from yellow to red. The dried stigmas reach up to1.5-3.5 cm in length. The dried stigmas have the upper part broader and slightly flattened while the plant end separates into a lean cone with an edge. The dried stigmas margins of the apex are irregularly dentate that have short slits at the inner side. The dried stigmas textures are bright, sloppy, and lenient [1,2,7]. The dried Stigma Croci odor is characteristic, aromatic, and slightly irritant. The dried stigmas taste pungent and slightly bitter [1,2,7]. The powdered Stigma Croci is orange or red. Stigma Croci powder is a little flowing and stripe-shaped. Stigma Croci powder has outer walls with papillae and indistinct fine striations. Papillose shape (26-56 μm in diameter) of Stigma Croci's apical cells are observed with scarce surface striations. Stigma Croci parenchyma is circular and possesses calcium oxalate (2-14 μm in diameter) [2]. *Crocus sativus* L. (Saffron) plant is valued worldwide for its potential use in managing many degenerative disorders such as cardiovascular diseases, cancer, immune disorders, diabetes, metabolic syndrome, neurodegenerative diseases, and sexual dysfunction. The crocetin, crocin, picrocrocin, and safranal are *Crocus sativus* L. ingredients that inhibit inflammation, oxidative stress, and apoptosis [8]. *Crocus sativus* L. plant and its active constituents exert beneficial effects against oxidative stress, inflammation, and apoptosis by inhibiting biochemical, inflammatory, and oxidative stress markers. Consequently, the *Crocus sativus* L. plant and its ingredients are included in new drug products for the treatment of ischemic stroke [9]. *Crocus sativus* L. plant extract protects against morphine-induced behavioral sensitization in rats through increasing serotonin levels [10]. *Crocus sativus* L. plant petal extract and *Crocus sativus* L. plant petal anthocyanins ameliorate symptoms of polycystic ovary syndrome by improving dysregulation of ovarian steroids, steroidogenic, anti-oxidant enzymes, and inflammatory markers in polycystic ovary syndrome mice [11]. Astragalin from *Crocus sativus* L. plant use in our daily meals helps fight against COVID-19 [12]. The bacteria test (gram-positive is more effective than gram-negative) uses Italian and Moroccan *Crocus sativus* stigma extracts [13]. *Crocus sativus* L. plant helps common people by increasing immunity and managing depression, stress, and anxiety caused by COVID-19 [14].

2. Chemical Constituents of Stigma Croci

Stigma Croci contains picrocrocin, safranal, and crocins ingredients [15-17] using colorimetric, spectrophotometric, and high-performance liquid chromatography techniques. *Crocus sativus* plant has its flavor, taste, color, and therapeutically profits as a result of its constituents (picrocrocin and crocin). Different forms of *Crocus sativus* L. obtained from Europe, Africa, and Asia revealed different constituents of *Crocus sativus* L., depending on the country's origin [18]. Treating plants with nitric oxide increases phenol and decreases flavonoid; however, phenol and flavonoid are increased by salinity. Therefore, picrocrocin and crocin are increased by nitric oxide [19]. One new compound (crocusatin M) and 3 new glycosidic compounds (crocusatins N-P), along with 9 known compounds, were isolated from the dried stigmas of *Crocus sativus* plant [20]. *Crocus sativus* plant didn’t contain colchicine ingredient in Stigma, flowers, and corms of the plant [21]. *Crocus sativus* L. and its ingredients protect the nervous cystem and increase neural activity [22,23].

3. Major Chemical constituents of Stigma Croci

The major constituents of Stigma Croci are 9 constituents as follows; (1) oils (0.4-1.3%), (2) 1,8-cineole, (3) α- pinene, (4) β-pinene, (5) picrocrocin (4%), (6) crocins (2%), (7) dimethylcrocetin, (8) safranal, and (9) crocetin [3,7].

4. Medicinal Uses of Stigma Croci

Stigma Croci has anti-oxidant effects in human studies [24]. Stigma Croci is used as a stimulant and protects from blood clots [25,26], and it causes relaxation and stimulates women's menstrual cycle [2,5]. *Crocus sativus* L. plant treats neuropsychiatric and neurodegenerative disorders and cancer [27]. Crocins ingredient of *Crocus sativus* L. plant is used to treat liver disease, cerebrovascular disease, neurodegeneration, diabetes, depression, cardiovascular disease, arthritis, and tumor [28]. Colchicine (isolated from autumn *Crocus sativus* L. plant) is used to treat many autoinflammatory diseases such as gout or familial Mediterranean fever. Colchicine is also used in the treatment of cardiovascular diseases. It is also tested in clinical trials for the treatment of COVID-19 [29].

5. Stigma Croci Uses in Traditional Medicine

Stigma Croci increases women's menstrual cycle, coughs, digestive ailments, abdominal pain, fever, depression, and pain associated with wounds [30,31]. Also, it is used as an aphrodisiac, contraceptive, diaphoretic, appetite stimulant, antispasmodic, and nerve sedative [30]. *Crocus sativus* L. plant treats inflammation, oxidative stress, tumors, depression, lower serum glucose and lipids, and memory disturbances; therefore, it is used to treat depression, memory conflicts, diabetes, Alzheimer's disease, anxiety disorders, and cancer [32]. *Crocus sativus* plant is used in traditional medicine to treat depression [33]. *Crocus sativus* L. contains several pharmacologically active substances, which provide new insight into managing COVID-19 infections and epidemics [34]. *Crocus sativus* L. is used as an alternative antidepressant to treat depression [35]. *Crocus sativus* L. is used in Traditional Persian Medicine to treat cutaneous leishmaniasis [36]. The crocin ingredient of *Crocus sativus* L. is used to treat psychological disorders [37].

6. Pharmacology of Stigma Croci

6.1. Experimental pharmacology.

6.1.1. Antiarteriosclerotic effect.

Consumption of saffron and resistance training improves blood pressure in the elderly with hypertension by affecting the factors involved in altering vascular endothelial resistance [38]. *Crocus sativus* Plant is used to treat hypertension and other cardiovascular diseases [39]. *Crocus sativus* Plant decreases serum lipids and protects from atherosclerosis-related diseases [40]. The crocetin injection for 1 month to rabbits fed a high-fat diet reduced both serum cholesterol and atherosclerosis by 50% and 30%, respectively, [41]. Decreasing serum lipids and hypolipidemia play an important role in human lipidome [42,43].

6.1.2. Anticoagulant activity.

The is no effect of *Crocus sativus* plant (200 and 400 mg) during 1 week on blood cloth [44]. The coagulation time of *Crocus sativus* is as follows; Stigma ethanolic extract (101.66 seconds) was almost equivalent to the standard drug (aspirin, 101.66 seconds), suggesting a strong anticoagulant effect followed by ethanolic petal extract (86.5 seconds). Leaf ethanolic extract (66.83 seconds) represented a moderate inhibitory effect on coagulation activity, while Corm ethanolic extract (42.83 seconds) showed a neutral effect [45].

6.1.3. Cell proliferation inhibition.

Stigma Croci (50-150 μg/ml/3 hours) decreased both tumor size and DNA synthesis by 25% and 50%, respectively, in cervical carcinoma (HeLa) cells in vitro [46,47]. The crocin and crocetin ingredients of Stigma Croci (0.8-2 μmol/l) stopped the growth of human acute leukemia cells in vitro [48]. The protein and nucleic acids in lung and cervical carcinoma, as well as, fetal human cell lines was completely stopped after administration with crocetin ingredient (35-55 μg/ml). Stopped the formation of DNA and protein in cancers [49]. The synthesis of DNA, RNA, and RNA polymerase II activity was declined in lung and cervical carcinoma and fetal human cell lines after incubation with crocetin [46]. Kaempferitrin flavonoid of *Crocus sativus* L. plant inhibits cell proliferation and apoptosis [50]. *Crocus sativus* L. plant inhibits liver cancer cell growth, arrests cell cycle in liver cancer, and induces cell apoptosis; therefore, the plant is used to treat liver cancer [51]. *Crocus sativus* L. has antiproliferative and antitumorigenic activities in osteosarcoma [52]. The crocetin ingredient of *Crocus sativus* L. has protective effects on human colorectal cancer HCT-116 cells, and this effect depends on the regulation of the *p*38 signaling pathway [53]. *Crocus sativus* L. plays an essential role in protecting against colon cancer through metabolome technique [54].

6.1.4. Central nervous system effect.

Injection of ethanol extract of Stigma Croci (125-250 mg/kg bw) has a relaxing effect on animals [55]. *Crocus sativus* L. reversed the depletion of glutathione in the injured brain. Moreover, *Crocus sativus* L. treatment reduced apoptosis as indicated by a decrease in caspase-3 and Bax protein expression, decreasing the apoptotic neuronal cells. Therefore, *Crocus sativus* L. treatment has neuroprotection by enhancing vascular endothelial growth factor [56]. *Crocus sativus* L. exerted a neuroprotective effect [57]. *Crocus sativus* plant is used as a neuroprotective product for neurodegenerative disorders, especially which implies dopaminergic and noradrenergic injuries, like Parkinson's disease, triggered by heavy metals [58]. *Crocus sativus* caused a decrease in neuronal injury by different mechanisms such as increasing superoxide dismutase and catalase activities, suppressing nuclear factor kappa B, interleukin-1, glial fibrillary acidic protein, and interleukin-6 expression. Consequently, *Crocus sativus* has a neuroprotective effect in central nervous system pathologies [59].

6.1.5. Chemical carcinogenesis inhibition.

Ethanol extract of Stigma Croci (100 mg/kg bw) in the form of ointment stopped skin tumors in animals [60]. Injection of Stigma Croci extract (100 mg/kg) daily for 30 days declined tissue tumor by 10% [60]. Stigma Croci extract at the same dose declined lymphoma and sarcoma tumors by 87% and 41%, respectively [31,60]. Crocin (400 mg/kg bw) declined

colon tumor and extend female life [61]. Stigma Croci extract (50 mg/kg bw) stopped the declines in white blood cells, hemoglobin, and body weight [62].

6.1.6. Circulation effect.

The water solution of *Crocus sativus* plant contains crocin ingredients that increase blood flow in the animal eye. Crocin (10 mg/kg bw) recovers eye function [63]. Crocin ameliorated cardiac tissues damage in periodontitis-induced cardiac damage. Crocin increases anti-oxidant enzymes in cardiac damage. Therefore, oxidative damage in cardiac tissue is improved by crocin [64]. *Crocus sativus* plant protects the heart, neurons, and memory. These effects are related to 2 carotenoids (crocin and crocetin). Crocin is an easy exit to urine from blood circulation. Crocin transfers to crocetin in the intestine; thus, crocin is in plasma is low—crocetin stores in higher quantities in body tissues. Crocetin accumulates in the central nervous system; thus, it treats neuron disorders. Feces removed higher crocin from the blood [65]. The infarct volume was decreased by 64%, 74%, and 73% after crocin exposure with 30, 60, and 120 mg/kg, respectively. Crocin (60 mg/kg) declined brain edema by 48%, 52%, and 51%, respectively.Therefore, crocin prevents brain edema and damage [66].

6.1.7. Anti-inflammatory activity.

Crocus sativus plant oral administration did not affect inflammatory cytokines [67]. *Crocus sativus* plant and its constituents increase immunoglobulin G but decrease immunoglobulin M, interleukin-10, and interleukin-4 secretion. Therefore, *Crocus sativus* Plant and its constituents are considered promising treatments for disorders associated with immune-dysregulation such as asthma and cancer [68]. *Crocus sativus* saponin significantly inhibited tumor necrosis factor-α)/ interferon-γ in carcinogenic human cells at 1 μM. *Crocus sativus* saponin lowered tumor necrosis factor-α)/ interferon-γ-induced gene expression [69]. *Crocus sativus* inhibits serum levels nuclear transcription factor κB, tumor necrosis factor-alpha, interferon-gamma, and some interleukin (IL) such as IL-1β, IL-6, IL-12, IL-17A. In addition, *Crocus sativus* down-regulates the key pro-inflammatory enzymes such as myeloperoxidase, cyclooxygenase-2, inducible nitric oxide synthase, phospholipase A2, and prostanoids [70]. *Crocus sativus* extract is similar to *Cupressus sempervirens* extract an anti-inflammatory effect [71].

6.1.8. Nootropic effect.

The alcohol extract of Stigma Croci improved learning and memory in learning-impaired mice [72]. Stigma Croci (125-500 mg/kg bw) extract inhibited learning disorder [55,73]. Injection of 250 mg/kg bw of Stigma Croci alcohol extract stopped inhibition of long-term potentiation in the dentate gyrus of rats [74]. Stigma Croci (250 mg/kg bw) improved impairments of learning behaviors. This effect was related to the crocin ingredient of Stigma Croci but not the crocetin ingredient [75]. Safranal (isolated from *Crocus sativus* L. plant) protects against neurotoxicity by modulating oxidative and apoptotic responses [76]. The crocetin ingredient of Stigma Croci treats Alzheimer's disease [77]. *Crocus sativus* L. has neuroprotective effects on cognitive impairment in patients with Alzheimer’s disease. The crocin ingredient of *Crocus sativus* L. appears to regulate glutamate levels and reduce oxidative stress [78]. *Crocus sativus* L. and crocin amend the chronic stress- dysfunction and oxidative stress in Alzheimer’s disease. The inhibitory effect of *Crocus sativus* plant is related to its

ability to inhibit inflammation and oxidative stress [79]. *Crocus sativus* L. and its bioactive components (crocins and safranal) exert a beneficial action in different central nervous system diseases such as anxiety, depression, epilepsy, and memory problems. *Crocus sativus* L. treats schizophrenia [80]. *Crocus sativus* plant treats psychological disorder (chronic and disabling mental disorder) [81]. *Crocus sativus* plant treatment and exercise increase serotonin and muscular neurotrophin-3 mRNA in the hippocampus compared to control [82]. *Crocus sativus* plant treats Alzheimer's disease [82]. Crocin ingredient of *Crocus sativus* plant during chemotherapy in breast cancer has alleviated anxiety and depression [83].

6.1.9. Cytotoxicity.

In vitro study, crocin ingredient of Stigma Croci had cytotoxicity on human and animal tumors with LD_{50} = 0.4 mmol/l and 1 mmol/l, respectively [63]. Stigma Croci, crocin, picrocrocin, and picrocrocin with LD_{50}= 2.3 mg/ml, 3 mmol/l, 3 mmol/l, and 0.8 mmol/l, respectively decreased tumor size. Crocin ingredients stimulate the apoptosis process [84]. *Crocus sativus* plant has antitumor activity on tumor cells without adverse effects on normal cells and prevents tumor formation. *Crocus sativus* plant appears to reduce the toxic effects of anticancer drugs. Consequently, *Crocus sativus* plant has a toxic effect on cancer cells, *Crocus sativus* plant extract is used to treat and prevent cancer, including nervous system cancer and common cancers [85].

6.2. Clinical pharmacology.

In a clinical study, 30 human cases were divided into 3 equal groups; healthy, patients (had coronary artery disease), and controls. Healthy and patient groups intake 50 mg of Stigma Croci in 100 ml of milk while controls intake milk only. All groups orally intake 2 times daily for 6 weeks. The lipoprotein declined by 42.3% and 37.9%, respectively, in healthy and patient groups. Therefore, Stigma Croci had an anti-oxidant effect in humans [24]. *Crocus sativus* L. plant declined serum cholesterol and glucose, diastolic blood pressure, waist circumference, and LDL cholesterol. *Crocus sativus* L. treats depression, mental, neural, and sexual disturbances [86]. *Crocus sativus* plant is important in establishing the proteomic balance inside the biological system in health and disease states [87]. *Crocus sativus* plant is used to treat disorders such as gastrointestinal disorders, especially in Asian countries where several studies reported the efficacy of this plant in the treatment of functional dyspepsia [88]. *Crocus sativus* plant treats skin diseases. Therefore, many lotions, creams, and cosmetics contain the *Crocus sativus* plant as a principal constituent [89].

7. Toxicity of Stigma Croci

The Stigma Croci lethal dose fifty equal to 20.7 g/kg bw in rats [31]. Stigma Croci ethanol extract exactly > 600 mg/kg bw in mice [90]. The dimethylcrocetin (taken from Stigma Croci) injected into mice did not exhibit hematological or biochemical toxic effects after intra-gastric injection up to 50 mg/kg bw [31].

8. Adverse Reactions of Stigma Croci

The lethal dose of Stigma Croci = 20 g. The smaller doses of Stigma Croci have undesirable side effects such as bleeding in many human areas such as the uterine, lips, nose,

eyelids, and urine. Stigma Croci also induces bloody diarrhea, vomiting, haematuria, numbness, vertigo, and yellow color in mucous membrane and human skin [5]. The oral administration with 5 g of Stigma Croci caused skin bleeding and blood clots [91]. Common side effects of *Crocus sativus* L. plant include diastolic blood pressure, vomiting, less appetite, and headache [86]. The most common toxic parts of *Crocus sativus* L. plant are seeds, followed by leaves and roots [92].

9. Contraindications of Stigma Croci

Stigma Croci causes uterine contractions; therefore, it is not used during pregnancy [5]. Oral intake with of Stigma Croci in kids, boys, teenagers, and lactating mothers is communicated with dietary habits. Bleeding disorders may cause stigma Croci.

10. Warnings of Stigma Croci

Stigma Croci (5 g or above) may cause uterine contractions and bleeding disorders. Stigma Croci high dose (12-20 g/day) may be fatal [6,30].

11. Precautions of Stigma Croci

11.1. Drug interactions.

The platelet aggregation was abolished by Stigma Croci inhibits. It must be used in patients with safety, especially patients treated with antiplatelet accumulation drugs and anticoagulant therapy.

11.2. Carcinogenesis, mutagenesis, impairment of fertility.

Stigma Croci extracts were not mutagenic in the *Salmonella* assay using strains TA98 and TA100 [93]. *Crocus sativus* L. plant and its ingredients (crocin and crocetin) have anti-migratory, anti-invasion, anti-angiogenic, and anti-metastatic activities. Crocin displayed more effective anti-metastatic potency than saffron extract and crocetin [94]. Crocin and dimethylcrocetin (1 mg/plate, 2 mg/plate, and 4 mg/plate) were not mutagenic in the *Salmonella* test using TA 1535 strain [31]. Stigma Croci (100 mg/plate) extract was not mutagenic in kidney or placenta cells [95].

11.3. Pregnancy: non-teratogenic effects.

Stigma Croci stimulates uterine contractions; therefore, it is not used during pregnancy [5].

11.4. Nursing mothers.

The use of Stigma Croci in kids, boys, teenagers, and lactating mothers depends on dietary habits with normal food use.

11.5. Paediatric use.

Stigma Croci may be caused by bleeding disorders.

11.6. Other precautions.

The data collected about the safety protocol of Stigma Croci with any drug or any laboratory interaction between Stigma Croci and any human cells, tissues, or organs revealed that Stigma Croci is completely safe. Also, Stigma Croci without any teratogenic effects on fetuses during pregnancy.

12. Dosage of Stigma Croci

Stigma Croci must be stored in the black closed metal box, away from light and moisture [5]. Stigma Croci is in 2 forms; dried stigmas or extracts of dried stigmas. The data collected about the consumption of Stigma Croci in standard food use quantities explored that Stigma Croci is completely safe [33,96]. The recommended therapeutic daily dose = 3-9 g [2]. However, owing to a report of toxicity = 5 g [91], doses below 5 g/day are recommended.

13. Conclusion

Stigma Croci refers to the dried stigmas of *Crocus sativus* L. plant, which belongs to the Iridaceae family. Stigma Croci is known as *Crocus officinalis* Martyn. Italy, France, Spain, China, and India are the main countries that include *Crocus sativus* L. plant. The powdered Stigma Croci is orange or red. Picrocrocin, safranal, and crocins are the main constituents of Stigma Croci. Traditional medicine proved that Stigma Croci is used to treating amenorrhoea, coughs, digestive ailments, abdominal pain, fever, depression, and pain associated with wounds. Pharmacology of Stigma Croci includes experimental pharmacology and clinical pharmacology. The lethal dose of fifty of Stigma Croci is equal to be 20.7 g/kg bw in rats while the LD_{50} of ethanol extract of Stigma Croci = > 600 mg/kg bw in mice. The dried stigmas and extracts are the 2 forms of Stigma Croci. Food that contains Stigma Croci is safe food, and doses below 5 g/day of Stigma Croci are suggested.

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Conflicts of Interest

The authors declare no conflict of interest.

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