



Crocus sativus Linn - A Potential Source for Diverse Therapeutic Applications

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ABSTRACT

The dried red stigma of *Crocus sativus* L. belonging to Iridaceae family is a variety of spice commercially named as Saffron. It consists of more than 150 volatile compounds chiefly the terpenes and their esters and it belongs to native of Greece and South west Asia. Saffron has the medicinally important activities such as anticancer, anti-inflammatory, antitussive, antioxidant, anxiolytic, aphrodisiac, antinociceptive, anticonvulsant, antihypertensive, antidepressant, antigenotoxic and relaxant activity. Literatures suggest extraction method like hydro distillation using cold, hot water and ethanol for collecting the active components of the leaves and flowers of *Crocus sativus* L. (saffron). The collected essential oil and other chemical constituents were investigated by the researchers by using GC/MS technique. The objective of this review is to highlight the salient features, biological activities and extraction methods for the active components of the plant.

Keywords: *Crocus sativus* L., antitumor, GC/MS, extraction, hydro-distillation.

INTRODUCTION

Crocus sativus L. is the botanical name of saffron which belongs to the family Iridaceae and has been cultivated in some countries such as India, Greece and also in Iran. The constituents such as picrocrocin and safranal which is present in the *Crocus sativus* L. are responsible for its bitter taste. The plant can grow up to 20-30 cm height and it consists of more than two vivid crimson stigmas in each flower in the repeating genus and species of *Crocus* and *Sativus*. The order of the saffron is Asparagales and it belongs to the class Liliopsida and division Magnoliophyta. The activities of *Crocus sativus* L. are such as anticancer, anti-inflammatory, antitussive, antioxidant, anxiolytic, aphrodisiac, antinociceptive, anticonvulsant, antihypertensive, cytotoxic effects, antidepressant, antigenotoxic and relaxant activity. It also helps in improving the learning and memory skills.¹ The *Crocus sativus* L. flower and stigmas are shown in (figure 1) and the year-wise production of saffron in Kashmir has been shown in (figure 2).

BIOLOGICAL ACTIVITIES OF *CROCUS SATIVUS* L.

Anticancer activity

Cancer refers to a disease that is due to an uncontrolled division of abnormal cells in the body. Julio Escribano *et al.*, (1996) was investigated to prevent the growth of tumor cells as well as to check the toxic level of compounds such as crocetin, picrocrocin, crocin and safranal from *Crocus Sativus* L. Among these compounds, the crocin which was treated with cancer cells had the good ability to prevent the growth of tumor cells. It was proved that crocin was the only compound which had the good therapeutic activity for cancer.²

F.I. Abdullaev *et al.* (2003) was evaluated the effect of *Crocus sativus* L. and its main ingredients on cytotoxic

effects using plate incorporation test and they found that the compound such as carotenoid as well as the saffron itself acts as the potential cancer hemopreventive agents.³



Crocus sativus L. flower Stigmas of *Crocus sativus* L.

Figure 1: *Crocus sativus* L. flower and stigmas.

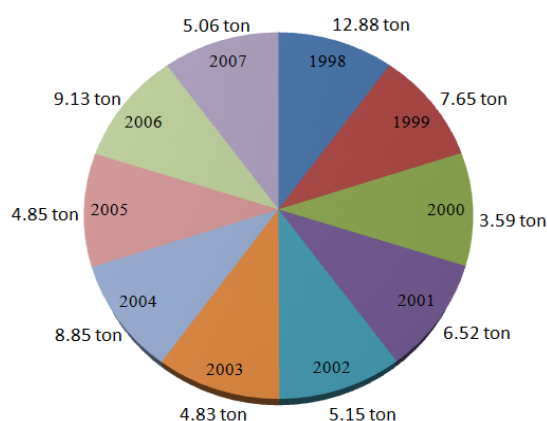


Figure 2: Year-wise trends in production of saffron in Kashmir.

Another study by Ila Das *et al.* (2010) evaluated the skin carcinogenesis effect for the chemopreventive action of aqueous saffron extract using the histopathological

approach. The saffron extract was treated before and after the induction of skin carcinogenesis in mice and proved that the saffron ingestion can inhibit the development of skin papillomas and also reduces its size. The results reported that the early treated dimethylbenz(a)anthracene (DMBA)-induced skin carcinoma by saffron proved to be a better chemotherapeutic agent.⁴

The cytotoxic effect has been checked for various extract of *Crocus Sativus L.* such as the extract of biological residues in ethanol:HCl, ethanol, hexane, dichloromethane, water:HCl and water. The action on cell viability and the composition in anthocyanins and flavonols were also examined. The result suggested that not all the extracts are cytotoxic at the lowest concentration of 900 µg/ml and the extract using water was said to be optimum for its food application due to the presence of its phenolic compound.⁵

Mild-to-moderate depression

Depression is typically the emotional illness which could extensively vary in its intensity. The common symptom of mild-to-moderate depression includes lack of energy, difficulty concentrating, depressed mood, sleep problems, poor stress tolerance appetite disturbance and anxiety. The treatment on mild-to-moderate depression has been carried out using the petal of *Crocus sativus L.* and was found that the efficacy as well as the application of petal *Crocus sativus L.* may be used as an alternative treatment for depression in traditional medicine.⁶

The patients who were suffering from depression after performing percutaneous coronary intervention (PCI) were compared for the efficacy and safety of saffron versus fluoxetine in improving depressive symptoms. Two groups of patients were treated with either fluoxetine or saffron capsule for 6 weeks and were examined. The results confirmed that the saffron capsules showed the same antidepressant efficacy compared with fluoxetine in patients.⁷

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 mortalities in mice after oral administration.⁸

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.⁹ Another study by C.D. Kanakis *et al.* (2009) 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 polynucleotide complexes.¹⁰

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.¹¹

Crush injury

A crush injury is an injury that occurs, when a body is compressed due to a high degree of pressure and force or due to natural disaster and that leads to crush syndrome. Esmael Tamaddonfard *et al.* evaluated the sciatic nerve function using safranal, the active constituent of Saffron after the induction of crush injury. Since, safranal had an antioxidant activity; vitamin E was used as a reference for antioxidant agent for which an intraperitoneal injection of vitamin E and the safranal were given for 10 consecutive days in rats. The results suggested that, both safranal and vitamin E had same developing effects on sciatic nerve function.¹²

Spinal cord injury

Spinal cord injury (SCI) is an injury which is caused due to trauma instead of disease and that damages the spinal cord and also the nerve roots. By using the animal model (Female Wister rats) Masoume Karami *et al.* was investigated the action of crocin in chronic pain. They found that the treatment on the chronic pain which is due to spinal cord injury can be prevented by crocin which decreases the calcitonin gene related peptide (CGRP) that is an important mediator of pain and inflammation.¹³

Retinal ischaemia/reperfusion (IR) injury

Retinal ischemia can occur due to insufficient blood supplementation to the retina or due to the lack of oxygen in the retinal and those results in reduced vision. Yun Qi *et al.* (2013) evaluated the neuroprotective action of crocin after the occurrence of retinal reperfusion injury on the retinal ganglion cells and it had been showed that the crocin could act through its P13K cell signalling pathways. The results suggested that, by activating the cell signalling pathway, the crocin could prevent the retinal reperfusion – induced apoptosis of ganglion cells.¹⁴

Menstruation syndrome

Menstruation syndrome is an irregular state of woman's menstrual cycle which includes dysfunctional uterine bleeding, amenorrhea, metrorrhagia, hypomenorrhea



and so on. Hajime Fukui *et al.* (2011) evaluated the first study to mainly clarify the action of saffron odour on the symptoms which is similar in women like dysmenorrhea (menstrual pain), irregular menstruation and premenstrual syndrome. The results revealed that the saffron odour could be effective in treating the menstrual distress in women.¹⁵

Neuronal injury

Neuronal injury is a cause of interruption in the nerve fibres or nerve cords and also the death of axon with or without the interruption to the endoneural tubes. Under serum free conditions, Takashi Ochiai *et al.*, was investigated in PC12 cells, the Growth Stimulating Hormone (GSH)-synthetic and antioxidant activities of crocins which has been caused only by crocin on the neuroprotective effects of *Crocus sativus L.* The results reported that crocin helps to promote the expression of mRNA than the carotenoid. The infarcted area which is affected due to the middle cerebral artery could be notably reduced by carotenoid.¹⁶

Myocardial injury

Myocardial injury refers to the acute myocardial infarction (AMI) and myocardial contusion to the heart. The cause of AMI is the formation of thrombus in coronary artery and the myocardial infarction is because of the extended ischemia. Jaspreet Sachdeva *et al.*, investigated, whether the extract of *Crocus sativus L.* exerts the myocardial damage induced by isoproterenol in male Wister rat. The result showed that, by maintaining the antioxidant status and structural integrity, the saffron exerted significant cardioprotective effect at all the doses by preventing hemodynamics and left ventricular functions.¹⁷

Lung Inflammation

Lung inflammation is caused by viral or bacterial infection that will lead to the formation of empyema, lung abscess and so on. Tuberculosis and pneumonia mainly causes the lung inflammation. The constituent such as safranal was investigated on differential and total white blood cells and lung pathology on guinea pigs.

The result confirmed that the lung inflammation on sensitized guinea pigs has been prevented by the *Crocus sativus L.* extract and the compound safranal showed good effect in an anti-inflammatory and anti-asthma mechanism.¹⁸

Aphrodisiac activity

An aphrodisiac is a substance that stimulates the sexual activity or sexual desire in human/animals, either by psychophysiological 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.¹⁹

Erectile dysfunction

Erectile dysfunction assigns a man's incapacity to retain an erection during sexual intercourse. Ali Shamsa *et al.* evaluated the effect of *Crocus sativus L.* on erectile dysfunction on male (human). The result confirmed that the saffron, only after taking it for ten days, it showed the beneficial effect in patients with huge number as well as duration of an erectile event.²⁰

Anxiety activity

Anxiety is an atypical sense of fear and apprehension due to tension, increased pulse, sweating and etc. It is also an unpalatable state of inner turmoil. Rat models were used in the study to check the anxiolytic properties in the presence of crocin and the authors N.Pitsikas *et al.*, found that the crocin which is the active constituent of *Crocus sativus L.* possess the anxiolytic-like effects in the rat.²¹

Anticonvulsant activity

Anticonvulsant is a drug which is used in the treatment of epilepsy and seizures. The main aim of this drug is to suppress an excessive firing of neurons which cause seizures. H.Hosseinzadeh *et al.* evaluated the compound safranal against seizures caused by pentylenetetrazol in rat model. The result revealed that the safranal could be used for an anticonvulsant activity in pentylenetetrazol model and this was mediated partly through gamma-aminobutyric acid (GABA_A) receptor complex.²²

Relaxant activity

Muscle relaxants are used to relieve the symptoms of muscle spasms, pain and hyper-reflexia which functions to decrease the muscle tone. The extract of *Crocus sativus L.* was obtained using aqueous-ethanol solvent mixture and the compound safranal present in saffron was analysed in guinea pig tracheal chains to check the relaxant activity of β -adrenoreceptors and it was found that the safranal possessed the partial effect on relaxant activity.²³

Arthritis

Arthritis is a condition of degenerative joint disorder which involves inflammation of one or more joints. Basically there is no cure for either rheumatoid or osteoarthritis. Medications can only help in reducing the inflammation in the joint and the joint damage could be slowed. The molecule crocin which is the active constituent of *Crocus sativus L.* was used in a study to investigate the antiarthritic potentiality and the carotenoid which has been isolated from the stigma of *Crocus sativus L.*

It has been reported that the serum levels of non-enzymatic, enzymatic and inflammatory mediators are neutralized by crocin. So, crocin could be considered as an effectual antiarthritic agent for the secondary complication of arthritis.²⁴

Hemi-parkinsonian



Hemiparkinsonism with hemiatrophy syndrome is a rare condition of parkinsonism featuring early onset of body hemiatrophy. Clinical features differentiating this condition from parkinson's disease are frequently associated action induced dystonia, slower progression and variable response to levodopa. Abdullah Shafique Ahmad *et al.*, evaluated the Parkinsonism on the rat model to check the neuromodulatory effects of crocetin in a 6-hydroxydopamine. The results showed that crocetin could prevent the Parkinsonism as well as the neurological disorder. The crocetin had also been used in various systems of indigenous medicine and it is an important diet ingredient.²⁵

Spatial memory deficit and oxidative stress

Upon extreme stress conditions, corticosteroids are released and on prolonged duration it leads to structural changes in the brain. These produces spatial memory as well as aggression. B.Naghizadeh *et al.*, evaluated the rat model to check the effect of crocin of *Crocus sativus L.* on cognitive performance in an oxidative stress. The report confirmed that the Alzheimer's disease which is the neurodegenerative disorders had the beneficial effects after treating with crocin.²⁶

Antagonize memory impairments

NMDA receptor antagonists and several synthetic opioids functioning as NMDAR antagonists are the class of anesthetics that work to antagonize are worked as anesthetics which can cause certain type of brain damage. Nikolaos Pitsikas *et al.*, evaluated the rat model to investigate the effect of saffron on memory and learning mechanisms. The report revealed that the

learning and memory mechanisms support the post training administration of *Crocus sativus L.* extract with the implication of *Crocus sativus L.*²⁷

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.²⁸

Cerebral Ischemia

Cerebral or brain ischemia is a condition that occurs due to insufficient blood flow to the brain to meet metabolic demand. Due to poor oxygen supply, brain tissues starts dying, known as cerebral infarction which leads to reduction in metabolic rates and energy crisis. The compound crocin which is isolated from saffron was evaluated for its therapeutic activity against brain edema, ischemic reperfusion injuries and also for an antioxidant activity. Abedin Vakili *et al.*, proved that the crocin could act against cerebral Ischemia and reperfusion injury in the rat model. Crocin also had an antioxidant activity by suppressing the creation of free radicals.²⁹

Hydro-organic extraction methods

Table 1: Different extraction methods of *Crocus sativus L.* using organic-aqueous and aqueous.

S.No	Extraction method	Solvent	Results	Author
1	Isopropanol – Aqueous extraction	Isopropanol – Aqueous	The triterpenoid saponins isolated from saffron was analysed on HeLa tumoral cells for its cytotoxic activity. ³¹	Ángela Rubio-Moraga <i>et al.</i> (2011)
2	Ethanolic aqueous extraction	Ethanol – Aqueous	The extraction was checked on long term potentiation and learning behaviour in mice and the effect was proved on crocin. ³²	H. Saitol <i>et al.</i> (2001)
3	Solid phase Extraction	Ethanol – Aqueous/Acetonitrile-Aqueous	Freeze drying extraction method increases the concentration of safranal whereas the extract by drying in rotary evaporator eliminates the safranal. ³³	A.V.Loskutov <i>et al.</i> (2000)
4	Ultrasound assisted extraction	Ethanol-Aqueous, Methanol-Aqueous	Recovery of crocin and picrocrocin using Response Surface Methodology (RSM) was determined. ³⁴	Anastasia Kyriakoudi <i>et al.</i> (2012)
5	Solid Phase Extraction	Aqueous	The compound picrocrocin was determined which could be useful in quality control of <i>Crocus sativus L.</i> spice in industries. ³⁵	Ana María Sánchez <i>et al.</i> (2009)
6	Maceration	Aqueous	The aphrodisiac activity was checked on crocin and safranal using male rats and has been proved. ³⁶	H. Hosseinzadeh <i>et al.</i> (2008)

Organic solvent extracts

Table 2: Different organic extraction methods of *Crocus sativus L.*

S.No	Extraction Method	Solvent	Results	Author
1	Cold percolation	Ethanol	Reduces snacking, as well enhances the satiety which contributes to weight loss. ³⁷	Bernard Gout <i>et al.</i> (2010)
2	Supercritical carbon dioxide extraction	Methanol	Confirms the presence of volatile compounds in the <i>Crocus sativus L.</i> using high performance liquid chromatography. ³⁸	P.Lozano <i>et al.</i> (2000)
3	Maceration	Ethanol	Constituents of safranal extract were checked for its lung inflammation in guinea pigs and it was proved to have anti-inflammatory effect. ³⁹	M.H.Boskabad <i>et al.</i> , (2012)
4	Micro extraction	Methanol and Acetonitrile	The compounds were identified using gas chromatography – mass spectroscopy (GC-MS) analysis. ⁴⁰	Hassan Sereshti <i>et al.</i> (2014)

Hematological and genotoxicity effect

Hematology is a study of blood and its related diseases. It includes studies related to pathology, diagnosis, treatment and prevention of blood diseases. Similarly, when an agent has a property to damage the genetic information within a cell leading to mutation and there by cancer, then it is said to be genotoxic. Alireza Timcheh Hariri *et al.*, evaluated the action of safranal and crocin against the subacute toxic level of diazinon on haematological and genotoxicity indices in rats and the result suggested that the effect of diazinon without cholinesterase showed decrease in toxicity but the genotoxicity induced by diazinon could not be prevented.³⁰

EXTRACTION METHODS OF *CROCUS SATIVUS L.*

The scientists have developed the various extraction methods using different solvents were shown in (table 1) and (table 2).

CONCLUSION

Crocus sativus L. belonging to the family Iridaceae and commonly known as saffron, is a well known herbal plant which is commercially available for culinary, body healing, detoxification and also in the spas. This review has highlighted its special biological activities such as anticancer, antioxidant, relaxant, anxiety, aphrodisiac activity and so on. Also the different extraction methods of *Crocus sativus L.* using various solvents such as aqueous, organic and aqueous-organic have been discussed. Recently, many research works are on-going in the area of formulation development and evaluation, to prove the significance of the plant products for medicinal application.

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