

Saffron (*Crocus sativus*) and its Active Ingredients: Role in the Prevention and Treatment of Disease

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ABSTRACT

Introduction: *Crocus sativus* is a member of iridaceae family and its use in health management is in practice since ancient time. Additionally, research based on clinical trials and animal models have advocates its role in disease cure without any severe adverse complications. The aim of this study is to summarize the study of saffron and its ingredients based on *in vivo* and *in vitro* and role in disease cure and prevention. **Materials:** This study was designed through the search engines such as Pub Med, Scopus and Google Scholar. The keywords used for the search were mainly focused on Saffron with health benefit and its therapeutics role in different diseases. **Result:** Saffron stigma is mixture of various components and recent studies have proven that saffron and its active ingredients play a key role in disease management. Moreover, clinical trials based study on the use of saffron and its individual components have confirmed the health promising effects. **Conclusion:** Although Saffron has potential role in the disease cure and prevention via modulation of anti-oxidant, anti-inflammatory, anti-tumour, anti-microbial and anti-diabetic activity. Furthermore, advanced research is needed to elaborate the role of saffron in health management and its mechanism of action in the modulation of biological activities.

Key words: *Crocus sativus*, Antioxidant, Anti-inflammatory, Anti-tumour activity, Toxicity level.

INTRODUCTION

Saffron is a spice of *Crocus sativus* (Saffron crocus) which belongs to the family of iridaceae¹ and studies has advocates its role in diseases cure. Its health management properties have been discussed in traditional prescriptions including Chinese, Ayurveda and Unani medicines. *Crocus sativus* has been reported its role as sedative, expectorant, anti-asthma, emmenagogue, and adaptogenic agent.² Different plant parts like peels, fruits, seeds and rind of *Crocus sativus* contain various biochemically active ingredients such as crocin, crocetin, and safranal in different proportion. These constituents have demonstrated the health promoting effect through the modulation of various biological and physiological processes.

The studies based on animal models and laboratory research has revealed that saffron has therapeutic implication in health management through anti-oxidant, anti-microbial, hepatoprotective and anti-tumour activity. Experiment finding confirmed that stigma ethanolic fraction showed the highest antioxidant activity possibly due to high content of phenolics and flavonoids³ and other studies have reported crocin role in inhibition of edema formation.⁴ Experiments have been performed to examine the mechanism of chemopreventive activity of this spice and the result of such study has revealed that saffron notably reduces

the increased number and incidence of hepatic dyschromatic nodules induced by diethylnitrosamine.⁵ Earlier studies reported that saffron is safe at various doses and did not show any severe side effects. Saffron aqua extract and pure crocin were safely tolerated in patients with schizophrenia.⁶ Study bases on evaluating the lactating toxicity and histological studies confirmed that saffron did not show any toxic effect on liver.⁷ This review is aimed to discuss the pharmacological activities of saffron as an antioxidant, anti-inflammatory, hepato-protective, cardioprotective, anti-diabetic and anti-tumour activity along with safe dosage levels based on clinical studies.

Chief ingredients of saffron

Saffron stigma is mixture of various components and such constituents have therapeutics importance in the health management through the modulation of various biological pathways. Saffron stigmas contain numerous volatile compounds and ingredients including crocin, picrocrocin and safranal and these compounds are accountable for color, taste and odor of saffron respectively.⁸⁻¹¹ Safranal is the major coloring constituent of saffron, so saffron is used as a flavoring and coloring agent.¹² In addition to these compounds,

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saffron also contains little amounts of other pigments like anthocyanin, α -carotene, β -carotene, and zeaxanthin.¹³

Possible mechanism of action of saffron and its ingredient in diseases prevention

The exact mechanism by which saffron and its constituents demonstrate the therapeutic role in diseases prevention is yet to be fully elucidated. Laboratory based research has revealed that saffron constituents modulate the activity of various enzymes involved in free radical scavenging. Moreover, these components reduce the lipid peroxidation and enhance the antioxidant status. Stigma ethanolic fraction of saffron showed the highest antioxidant activity that might be recognized due to the presence of phenolics and flavonoids.³⁻¹⁴ Other experimental data advocates that saffron helps in reduction of inflammation through the inhibition of cyclooxygenase enzyme activity. Saffron alleviates neuropathic pain via reduction of proinflammatory cytokines, antioxidant activity and apoptotic pathways¹⁵ and *in vitro* study has revealed that crocin possess dual inhibitory activity against COX-1 and COX-2 enzymes.⁴ Saffron also shows a very important role in the tumour prevention and some findings advocate that saffron and its constituents induce apoptosis or change the ratio of bcl2/bax and finally inhibiting the development and progression of tumour.

LD₅₀ Safety and toxicity level of saffron and its ingredient

A study based on mice model revealed that LD₅₀ value of saffron was 4120 \pm 556 mg/kg⁷ and correspondingly, LD₅₀ of safranal, a constituent of saffron is reported to be 1.48 mL/kg and 1.88 mL/kg in male and female mice respectively.¹⁶ Other study based on mice models have reported that, LD₅₀ values of saffron stigma and petal extracts were 1.6 and 6 g/kg respectively in.¹⁷ In addition to this, saffron aqua extract and crocin have been found to be safely tolerated in patients with schizophrenia.⁶ Safranal, an ingredient of saffron was less-toxic in acute intraperitoneal route and non-toxic in acute oral administration in mice and rats.¹⁶ However, in sub acute toxicity tests, safranal showed alterations in hematological and biochemical parameters.¹⁶ Saffron tablets have proven that it showed a little change in hematological as well as biochemical parameters but such changes were within normal ranges.¹⁸ Rat model based study for sub-acute toxicity revealed that saffron showed increased survival and no mortality rates at a dose of 10 mg/kg.¹⁹ Saffron has confirmed it did not show toxic effect on liver whereas histo-pathological changes were noticed in the neonate kidneys.⁷ Moreover, earlier study has reported that the injection dose between 1.2 g and 2 g of saffron may cause some complications including nausea, vomiting and, diarrhea.²⁰

Clinical studies on saffron and their constituent

Clinical trials based on the use of saffron and its individual components have confirmed the health promising effects. Double-blind study performed on patients, who were randomly allocated to receive saffron or imipramine capsule, have revealed that the dose of saffron is efficiently similar to imipramine in the treatment of mild to moderate depression.²¹ In another similar pilot study, forty adult outpatients were randomly assigned to get capsules of saffron or fluoxetine and the results revealed that fluoxetine is similar in the treatment of mild to moderate depression.²² Schizophrenic cases were used to study the safety and tolerability of saffron aqueous extract and crocin and the results of the study have revealed that none of the patients showed any severe side effects.⁶ WBC count was found to increase within a limited range in patients that getting saffron aqua extract and those patients did not show any clinical significance.⁶ Randomized, double-blind, placebo-controlled study design consisting of one-month treatment of crocin tablets have

confirmed that no major unfavorable effect was noticed during the trial.²³ In a similar study performed on double-blind, placebo-controlled patients getting a capsule of saffron or placebo capsule for a six-week study. *Crocus sativus* showed significantly better outcome on the Hamilton depression rating scale and there were no significant differences observed in the two groups in terms of the side effects.²⁴

Pharmalogical activities of saffron

Anti-oxidant activity

The imbalance between reactive oxygen species (ROS) production and antioxidant level is directly linked to the pathogenesis of diseases. The enhancement of antioxidant level or reduction of reactive species level is maintained through antioxidant properties of plants or their derivatives. Natural products or derivatives of medicinal plants usually contain various components including flavonoids which show a pivotal role as antioxidants and free radicals scavenging activity. Numerous studies based on *in vivo* and *in vitro* have confirmed that *Crocus sativus* has a significant antioxidant activity Table 1.

Antioxidant activity of saffron has been observed in extract of stigma and such extract shows role in the reduction of chlorophyll damage, lipid peroxidation, and protein oxidation.³ Similarly, other finding has confirmed that saffron stigma contains superior antioxidant activity.¹⁴ Earlier findings have demonstrated that active and inactive constituents of saffron extract have high antioxidant activity²⁵ and saffron petal extract showed antioxidant activity.²⁶ Another study demonstrated that constituent of saffron such as crocin has a potent antioxidant activity.²⁷ Lebanon based finding demonstrated that saffron notably decreased lipid peroxidation as well increased superoxide dismutase activity when compared to control group.²⁸ Crocin, constituent of saffron showed role in the inhibition of lipid peroxidation and restored SOD activity²⁹ and stigmas of *Crocus sativus* contains more antioxidant activity as compared to tomatoes and carrots.³⁰

Anti-inflammatory effect

Natural product based treatments for migraine, pain, inflammation and arthritis are very popular in traditional medicine due to easily availability and almost no side effects properties. In this regard, *C. sativus* has also proven its role as an anti-inflammatory Table 1. A study was performed on mice models to evaluate its anti-inflammatory activity and the results revealed that extracts of stigma and petal of saffron showed anti-inflammatory activity.³¹ In a parallel study results demonstrated that ingredients of saffron such as crocin and safranal suppressed inflammatory pain response as well and decreased the number of neutrophils.³²

Anti-microbial activity

Multi-drug resistant microorganism to antibiotics is alarmingly rising worldwide. As a treatment module against microorganism, natural products or derivatives of medicinal plants represent a symbol of good source of antimicrobial agents without any adverse side effect. Different parts of *Crocus sativus*, such as stamen and corolla have been employed as a good source of antimicrobial agents.³³ Extracts of *Crocus sativus* against various bacterial strains have confirmed an improved activity against bacteria and fungi used as test organisms.³⁴ In addition, antibacterial effects of other blends like aqueous, ethanolic and methanolic extracts of petal were measured against the foodborne pathogens and the results have confirmed that such extracts show antimicrobial activity against most of the pathogenic bacteria.³⁵

Hepatoprotective effect

Parts of medicinal plant like flowers, leaves, stem, roots and seeds have been found to possess a good hepato-protective activity. In this vista,

Table 1: Pharmacological activities of saffron and its constituents.

Reference	Biological activity	Aim of study	Finding /Outcome
[14]	Antioxidant	Evaluation of antioxidant activity of stigmas extract	Saffron stigma showed antioxidant activity.
[26]	Antioxidant	Measurement of antioxidant	Antioxidant activity has been observed.
[32]	Anti-inflammatory	Effects of crocin, safranal on local inflammation	Study finding reported that crocin and safranal showed role in the suppression of inflammatory pain responses and decreased the number of neutrophils.
[4]	Anti-inflammatory	Anti-inflammatory effects of crocin	Crocin, a constituent showed anti-inflammatory effects and modulate inflammatory processes.
[33]	Antibacterial	<i>C. sativus</i> extract tested against bacteria.	Strong activity of against bacteria and fungi was noted.
[36]	Hepatoprotective	Evaluation of protective effects of extract against hepatotoxicity	Finding demonstrated that petals ameliorate acute liver injury.
[40]	Protective effect against nephrotoxicity	Effect of safranal against nephrotoxicity	Safranal has a protective effect against nephrotoxicity.
[42]	Cardio-protective	Cardio-protective effect of saffron and safranal.	Result revealed that myocardial injury preserved nearly normal tissue architecture with saffron or safranal pretreatment.
[49]	Inhibitory action on AChE	Inhibitory action on AChE via saffron extract and its constituents.	Result indicated that Saffron extract showed moderate AChE inhibitory activity.
[53]	Anti-hyperglycemic	Saffron, crocin and safranal effects on the blood levels of fasting glucose, HbA1c and liver/kidney function tests	Result demonstrated that saffron extract, crocin and safranal significantly reduced the fasting blood glucose levels but significantly increased the blood insulin levels in the diabetic rats compared with the control diabetic rats.
[56]	Anti-obesity and anorectic	Effects of saffron and crocin on body weight, food intake and blood leptin levels.	Result concluded that saffron has anti-obesity and anorectic effects and lowered leptin levels.
[57]	Anti-obesity	Evaluation of anti-obesity effects of saffron and crocin	Result showed that saffron extract significantly decreased food consumption in obese rats. Furthermore, crocin showed a significant decrease on rate of body weight gain.
[58]	Aphrodisiac activities	Aphrodisiac activities of stigma and safranal and crocin.	The study results revealed that aphrodisiac activity of saffron extract and its constituent crocin.
[60]	Anxiolytic properties	Evaluation of anxiolytic and hypnotic effect of saffron extract, crocin and safranal.	Results confirmed safranal at higher doses demonstrated anxiolytic effects whereas crocin did not show anxiolytic properties.
[62]	Immuno-stimulatory	Effects of saffron petal extract on blood parameters and immune system	Saffron petal extract use causes an increase in antibody response
[64]	Anticonvulsant	Evaluation of anticonvulsant of safranal and crocin	Finding confirmed that safranal reduced the seizure duration, delayed the onset of tonic convulsions

saffron has also been checked for the liver ailments which possible improve or decrease various liver enzymes activity Table 1. Increases level of ALT, AST and bilirubin level and lowering total protein and albumin production was observed in acetaminophen treated rat models whereas pretreatment of rats with *Crocus sativus* petals extract resists this rise of aminotransferases and bilirubin levels and normalize the level of serum proteins as compared to disease control.³⁶ Results of findings have confirmed that saffron and honey showed role in the reduction of toxic effects of aluminum chloride and alleviate its disrupting effects at biochemical and molecular levels³⁷ and other results have confirmed that this ingredient of saffron definitely reduces the oxidative stress and prevents hepatotoxicity.³⁸

Nephrotoxicity effect

In this regard, crocin from saffron has also been tried by some researchers to survey its role against renal problems. It has been observed that this compound obstructs the development of acute renal failure and oxidative stress in experimental animals.³⁹ In a parallel study, safranal has been found to possess a protective effect against nephrotoxicity^{40,41}

Cardio-protective effect

Several medicinal plants have been used for the treatment of heart ailments since ancient times. In this vista, saffron and its constituents have also supported the evidences of cardio-protective effects. Rat model based study has confirmed that whole saffron pretreatment or its individual constituents such as safranal pretreatment considerably decrease the serum LDH and CK-MB level, as well as myocardial lipid peroxidation as compared to isoproterenol – induced animals.⁴² Crocin, an ingredient of saffron revealed its protective effects of cardio-toxicity through reducing lipid peroxidation as well as alleviating apoptosis.⁴³

In a similar study based on rat models, it was concluded that crocin improves toxic effects of diazinon through decreasing lipid peroxidation and restoring altered contractile and relaxant responses in aorta.⁴⁴ The cardio-protective effect of saffron active constituents including crocin has been confirmed through regulation of oxidative stress.⁴⁵ The finding concluded that *Crocus sativus* perfused during electrolysis might trap radical oxygen species and significantly improve myocardial function.⁴⁶

Neuroprotective effect

Crocine has been examined for its role against cytotoxicity effects. In this scenario, it has been observed that pretreatment of groups or cells with crocine protected them from acrylamide-induced apoptosis via inhibition of intracellular ROS production.⁴⁷ Furthermore, pretreatment of numerous dopaminergic cells of substantia nigra pars compacta from mice and retina of Parkinsonian cases were investigated for acetylcholinesterase inhibitory activity by saffron and it was observed that saffron ingredient, crocine actively exhibits this activity.^{48,49} Crocine also attenuates the learning and memory impairment in streptozotocin injected animal groups.⁵⁰

Anti-diabetic activity

The extract of saffron has been found to be effective in reducing fasting blood glucose in mild diabetic and in severely diabetic rats.⁵¹ Other findings demonstrated that saffron with dose of 40 and 80 mg/kg significantly increased body weight and serum TNF- α and decreased blood glucose levels and glycosylated serum protein levels.⁵² In one more study, it was found that methanolic extract of saffron, crocine and safranal notably reduce the fasting blood glucose and HbA1c levels.⁵³ Similarly, further study indicates that crocine, was found to significantly reduce the blood glucose level.⁵⁴ Oral administration of saffron extract was found to significantly increase the body weight and regulates the serum insulin level in diabetic rats as compared to disease control groups.⁵⁵

Anti-obesity effect

Earlier investigations concluded that Saffron showed anti-obesity and anorectic effects in the obese rat models. Moreover, its property of reducing the leptin level in obese cases indicates that saffron reduces fat mass and increases insulin sensitivity.⁵⁶ In an experimental protocol, it was performed to assess the anti-obesity effects of ethanolic extracts of saffron and crocine. Results of this study demonstrated that saffron extract notably decrease the food consumption by obese rats as compared to control groups. Furthermore, crocine showed a noteworthy decrease on rate of body weight gain, total fat deposition and regulates the weight ratio of epididymal fat to body.⁵⁷

Aphrodisiac activities

Saffron also plays an important role in improving the fertility and increases the libido when consumed. Results have revealed that crocine and its aqueous extract particularly at doses of 160-320 mg/kg b.w. increased mounting and erection frequency behaviors and in addition to this reduced ejaculation, intromission and mount latency parameters.⁵⁸

Anxiolytic activity

A study was performed to examine whether or not crocine, a major constituent of saffron hold anxiolytic activities. Either crocine which did not influence animal's motor activity or diazepam notably increased the latency to enter the dark compartment. The study designates that treatment with chief ingredients of *Crocus sativus L.* induces anxiety relieving effects in the rat⁵⁹ and safranal at higher dosage demonstrated anxiolytic effects and furthermore, safranal increased the total sleep time dose dependence.⁶⁰

Immunomodulatory effect

Earlier finding has supported the role of saffron in improving the immune system and it was shown that saffron increased the IgG level and decreased the IgM level as compared with the baseline and placebo groups.⁶¹ In addition to this, it increases the percentage of monocytes as compared with placebo.⁶¹ Other study concluded that saffron petal extract causes an increase in antibody response without any alteration in hematological parameters or histology of spleen.⁶²

Effect on retinal function

Results have positively confirmed from a study that analogue of *Crocus sativus* were found to significantly increase the blood flow in the retina and choroid and enhance the retinal function recovery.⁶³

Anticonvulsant effect

Experiments based on mice were performed to evaluate the anticonvulsant activities of safranal and crocine and the results indicate that safranal reduced the seizure duration, delayed the onset of convulsions as well as

Table 2: Anti-tumour activity of saffron and its ingredients.

Reference	Tumor/Cell type	Aim of study	Finding
[68]	Sarcoma-180, Ehrlich ascites Carcinoma and Dalton's lymphoma	Antitumor activity of saffron	Study finding demonstrated that oral administration of extract increased the life span of S-180, EAC, DLA tumour bearing mice
[70]	Transitional cell carcinoma	Cytotoxic effect of extract of saffron	Study concluded that saffron extract has inhibitory effects on the growth of both TCC as well as normal cell lines.
[72]	Colorectal cancer	Anti-proliferative effects of <i>Crocus sativus</i> extract and crocine	Data from this study demonstrated that <i>Crocus sativus</i> extract and crocine, significantly inhibited the growth of colorectal cancer cells
[74]	Hepatocarcinoma	Antiproliferative Effects	Study finding revealed that telomerase activity of HepG2 cells decreases after treatment with crocine
[75]	Malignant and nonmalignant prostate cancer cell	Antiproliferative effects of saffron extract and crocine	Based on result study concluded that both saffron extract as well as crocine can inhibit cell proliferation and arrest cell cycle progression
[77]	Prostate cancer	Cytotoxic and apoptosis induction	Finding based on result demonstrated a prostate cancer cell line to be highly sensitive to safranal-mediated growth inhibition and apoptotic cell death.
[76]	Skin carcinoma	Chemopreventive effect of aqueous saffron	Study result concluded that saffron inhibits skin carcinoma in mice when treated early.
[77]	Lung cancer cells	Potential of saffron to induce cytotoxic and apoptotic effects	Finding demonstrated that proliferation of the A549 cells was decreased after treatment with saffron
[79]	Human pancreatic cancer	Designed to elucidate apoptosis induction by crocine	Crocine induced apoptosis and G1-phase cell cycle arrest

protected mice from death.⁶⁴ This study further investigated that crocin did not show this anticonvulsant activity at all.⁶⁴

Anti-tumour activity

It is very well known that medicinal plants such as curcumin, ginger, carica papaya and black seed have therapeutic role in the management of numerous diseases including tumour.⁶⁵⁻⁶⁷ Saffron and its active constituents perform an important role in the inhibition of tumour development and progression Table 2. In this regard, numerous findings based on animal models confirmed that saffron plays a role in prevention of various types of tumour. Saffron extract via oral administration show increased life span of sarcoma -180, Ehrlich ascites Carcinoma and Dalton's lymphoma ascites tumour bearing mice.⁶⁸ Earlier findings reported that crocetin, an ingredient of saffron intensively reverted back the pathological changes noticed in cancerous animals⁶⁹ and other finding concluded that saffron aqueous extract shows inhibitory effects on the growth of both transitional cell carcinoma and normal cell lines.⁷⁰

Either intraperitoneal administration of *Nigella sativa* or oral administration of saffron after subcutaneous administration of MCA showed restriction of tumor incidence as compared with % MCA-treated controls.⁷¹ Anti-proliferative effects of saffron extract and pure crocin was examined on colorectal cancer cell lines. The result of this study revealed that both the extracts, significantly inhibited the growth of colorectal cancer cells whereas it did not affect normal cells.⁷² Furthermore, cytotoxicity and DNA-adduct formation of microsomes activated by aflatoxin B1 in the fibroblast cells were noticeably inhibited by crocetin pretreatment.⁷³ A finding showed that telomerase activity of HepG2 cells decreases after treatment with ingredient of saffron including crocin⁷⁴ Antiproliferative effects of saffron extract and individual constituent like crocin was evaluated on various malignant and non-malignant prostate cancer cell lines. Results based on these findings reported that crocin reduced proliferation in all malignant cells whereas nonmalignant cells were not affected at all.⁷⁵

In addition to this, another experiment was performed to investigate the chemopreventive effect of aqueous saffron. The result of the studies reported that saffron ingestion inhibited the formation of skin papillomas and simultaneously reduced their size in animals.⁷⁶ Furthermore, investigation has been done on the role of saffron to induce cytotoxic and apoptotic effects in lung cancer cells. The results of the study have revealed that proliferation of such cells was decreased after treatment of saffron in a dose- and time-dependent manner.⁷⁷ Moreover, saffron induced morphological changes, decreases percentage of some viable cells, and induce apoptosis.⁷⁷ Result of study revealed that crocin inhibited cell proliferation and induced apoptosis and cell cycle arrest at G₀/G₁ phase. Moreover, crocin inhibited the tumor weight as well as size of xenografts in nude mice. In addition to this Bcl-2 expression was inhibited and Bax expression in xenografts was increased.⁷⁸

In another important study, performed on human pancreatic cancer cell line to elucidate apoptosis induction by crocin and the results of this study reported that crocin induced apoptosis and G1-phase cell cycle arrest.⁷⁹

CONCLUSION

These days the popularity of alternative medicines based treatment is gaining much interest in the health practice. Saffron has shown its role in disease prevention and treatment and its importance in disease cure have been documented. Moreover, it is believed to be a safe and its adverse effect was not noticed at various doses. In addition, mortality was not noticed in animal model experiments at different dosage of individual ingredient of saffron. The role of saffron including crocin and crocetin in the management of numerous diseases has proven via modulation of

various physiological and biochemical pathways. Saffron has also been reported to exhibit an anti-tumour effect through inactivation or activation of different molecular cascades. Research based on animal models and clinical trials are further needed to expand the understanding of saffron and its constituent's role in diseases prevention.

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CONFLICT OF INTEREST

There is no conflict of interest.

ABBREVIATION USED

COX: Cyclooxygenase; **ROS:** Reactive Oxygen Species; **ALP:** Alkaline Phosphatase; **TCC:** Transitional Cell Carcinoma; **SOD:** Superoxide dismutase; **TNF - α :** Tumor necrosis factor; **LD:** Lethal dose.

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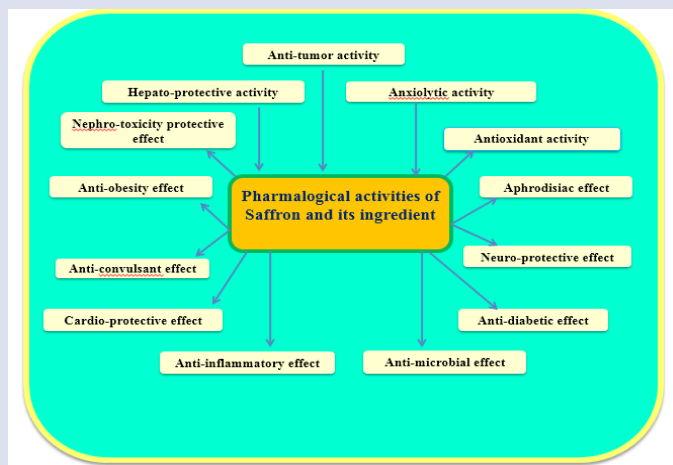
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GRAPHICAL ABSTRACT



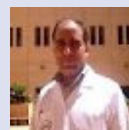
SUMMARY

- *Crocus sativus* is a member of iridaceae family and its use in health management is in practice since ancient time.
- Saffron stigma is mixture of valuable components including crocin, crocetin and safranal.
- Research based on clinical trials and animal models have advocates its role in health management without any severe adverse complications.
- Additionally, it also shows role in tumour management through modulation of cell signaling pathways.

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