

Therapeutic effects of *Crocus sativus*: An overview of systematic reviews

Hojat Rouhi Boroujeni¹, Sara Kiani^{2*}

¹Student, Student Research Committee, Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, I.R. Iran; ²Research Assistant, Shahrekord University of Medical Sciences, Shahrekord, I.R. Iran.

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ABSTRACT

Background and aims: *Crocus sativus* is of medicinal plants possessing many beneficial effects in treatment of various disorders. This study aimed to overview the therapeutic effects of *Crocus sativus* on the basis of reviews and systematic reviews.

Methods: Computerized search of review articles was performed using PubMed, Google Scholar, Scopus and Web of Science, Medline database from 1996 to 2015.

Results: Searches identified 8 reviews and systematic reviews of therapeutic effects of *Crocus sativus*. Despite remarkable difference in interventions, and type of studies carried out on this plant (in vivo and in vitro), it seemed to have many therapeutic effects on the treatment of various types of diseases. In all the reviews, the objectives were similar, e.g. inhibition of growth of cancer cell lines, analgesic activity, improvement of health condition and treatment of some disease but the type of study (in vivo and in vitro) (animal studies: rat, mouse, guinipig, rabbit) and content was quite different. The most common effects of *Crocus sativus* were anti-carcinogenesis, tumoricidal, anti-depressant, antihypertensive, anticonvulsant, antitussive, anti-genotoxic and cytotoxic effects, anti-Alzheimer's, antitussive, anxiolytic, aphrodisiac, antioxidant, anti-nociceptive, anti-inflammatory, relaxant activity, and effects on the gastrointestinal tract, on ocular blood flow and on retinal function, effect on coronary artery diseases, and hypnotic, and anesthetic effects.

Conclusion: The results of various studies on *Crocus sativus* showed that it has a lot of therapeutic effects on the treatment of various types of diseases. However, to be able to use these results in our daily life, additional clinical trials with larger sample size and longer duration may be required to evaluate its toxicity and safety in each and every case of its therapeutic effects.

Keywords: *Crocus sativus*, Therapeutic effects, Medicinal plants.

INTRODUCTION

Crocus sativus, the dry stigmas of the plant *Crocus sativus* L., are belonging to the Iridaceae family and it is principally native to Iran and Spain.^{1,2} The chemical constituents of *Crocus sativus* include the carotenoids, crocins and crocetin,

picrocrocin, safranal and the monoterpene aldehydes.³⁻⁵ In addition, it includes proteins, sugars, vitamins, flavonoid, amino-acid, minerals and gums.^{1,6} Anti-carcinogenic activity,^{4,7-18} anti-tumor properties,^{10-12,15,19} its cytotoxic effects,²⁰ and

*Corresponding author: Research Assistant, Shahrekord University of Medical Sciences, Tel: 00989140204896, E-mail: kiani.sandra@yahoo.com

anti-depressant activity²¹⁻²⁶ of this plant has been shown in number of studies. The mechanism of action for the effects of *Crocus sativus* has been attributed to its inhibitory effect on the synthesis of DNA and RNA,⁸ ability to scavenge of free radicals,^{15,16} involvement in the metabolic conversion of carotenoids to retinoid,²² mediation of interactions of carotenoids with topoisomerase II, an enzyme involved in cellular DNA-protein interaction,¹⁴ promotion of interactions mediated via lectins,²⁷ drug-metabolizing enzymes,²⁸ inhibition of nucleic acid and free radical chain reactions,¹⁸ inducing of apoptosis in tumor cells.²⁹ It has been indicated that carotenoids in *Crocus sativus* delayed the ascites tumor growth and increased the life span of the treated mice compared to the untreated controls by 45-120%.¹⁵ It delayed the growing of papilloma, decreased the rate of cell carcinoma incidence and soft tissue sarcoma.¹⁵ The present study was aimed at providing a comprehensive and systematic overview of the potential underlying anticancer, anti-tumor and cytotoxic effects and activities and the mechanism of actions of *Crocus sativus*.

Phytochemical compounds: Chemical analysis of *Crocus sativus* stigmas has shown that there are 150 volatile and nonvolatile compounds.³⁰ This compounds consist of lipophilic and hydrophilic carbohydrates, proteins, amino acids, minerals, mucilage, vitamins and pigments including crocin, anthocianin, carotene, lycopene, zizgantin, flavonoid, starch, gums and other chemical ingredients.² Carotenoids that consist of crocin, crocetin, the monoterpene aldehydes, picrocrocin and safranal were shown to be the most important secondary ingredients of *Crocus sativus*. Crocin is hydrophilic carotenoids. Deep red color of crocin produces the color of *Crocus sativus*. Crocin is widely used as a natural food colorant.³¹ In addition to crocin,

Crocus sativus contains crocetin, anthocianin, α -carotene, β - carotene, and zizgantin.³² Crocetin, which is responsible for the color of *Crocus sativus*, is of natural carotenoids Picrocrocin, responsible for the taste of *Crocus sativus*, is the main bitter component of *Crocus sativus*.³³ Safranal, responsible for the aroma of *Crocus sativus*, is the main volatile oil.³² The stability status of *Crocus sativus* and its ingredients rely upon temperature, light and humidity.³⁴

In view of its wide range of medical uses, the *Crocus sativus* has undergone extensive phytochemical and biochemical studies and a variety of biologically active ingredients has been isolated. Characteristics of many of its non-volatile active components are including carotenoids such as zeaxanthine, lycopene, and various α - and β -carotenes.³⁵ The odorous volatiles components of *Crocus sativus* are mainly terpenes, terpene alcohols, and their esters.³⁶ Non-volatiles components of *Crocus sativus* include crocins that together with carotenes, crocetin, and picrocrocin are responsible for the red color of stigmas.³⁷ However, the golden yellow-orange color of *Crocus sativus* is primarily due to α -crocin. This crocin is trans-crocetin di-(β -D-gentiobiosyl) ester. Crocetin is an oil soluble conjugated acid that is hydrophobic. During hydrolysis, Crocin produces gentiobiosyl and crocetin, meanwhile picrocrocin produces glucose and safranal.³⁶ Flavor of *Crocus sativus* is the result of the bitter taste of glucosidein picrocrocin. Dry *Crocus sativus* is highly sensitive to light and oxidizing agent and it breaks down immediately. As a result, it should be kept in air-tight containers.

METHOD

Computerized search of published articles was performed using PubMed, Google Scholar, Scopus and Web of Science, Medline databases as well as local

references from 1996 to 2015. The search terms used in this study were *Crocus sativus*, therapeutic, pharmacological effects. Additional sources were identified through cross-referencing.

The initial search strategy identified about 273 references. In this study, it was accepted 100 studies for further screening and 8 reviews met all our inclusion criteria (in English, full text, therapeutic effects of *Crocus sativus* and dated mainly from the year 1996 or later).

RESULTS

The reviews include 7 reviews including systematic reviews, and one meta-analysis. The reviews were included the following reviews with following therapeutic effects of *Crocus sativus*: Anti-carcinogenic properties of *Crocus sativus*,³⁸ cancer chemoprevention and tumoricidal properties of *Crocus sativus*,¹⁰ anti-tumor properties of *Crocus sativus*,³⁹ comprehensive review of therapeutic effects of *Crocus sativus*⁴⁰ covering antihypertensive activity, anticonvulsant activity, antitussive activity, antigenotoxic and cytotoxic effects of *Crocus sativus*, effect on sexual behavior, anxiolytic activity, relaxant property, effect on depression, effect on learning behavior and long-term potentiation, effects on ocular blood flow and retinal function, effect on coronary artery disease, anti-nociceptive and anti-inflammatory effects, and one meta-analysis covering anti-major depressive disorder (MDD),²¹ Avicenna's (IbnSina) the canon of medicine and *Crocus sativus*,⁴¹ and an update review of *Crocus sativus*,⁶ and clinical applications of saffron.⁴²

Our review was indicated that 7 of the 8 reviews were descriptive^{6,10,18,38-41} and one had performed meta-analysis.²¹ Anti-cancer effects were the most frequently reported effect of the *Crocus sativus*.^{4,7-18} In 5 of 8

reviews, anti-tumor effect of *Crocus sativus* was mentioned,^{10-12,15,19} but not in the meta-analysis. 5 of 8 studies was shown antidepressant effect of *Crocus sativus*.^{22,36-38} The meta-analysis study showed a significant positive effect on anti-major depressive disorder.²¹ 2 of the 8 reviews had mentioned anticonvulsant activity.³⁷ Effects on cardiovascular diseases had been investigated in 2 reviews,^{37,38} but the mechanisms of action remained unclear.

Two of seven descriptive reviews supported that *Crocus sativus* had anti-nociceptive and anti-inflammatory effects.³⁶⁻³⁸ Antitussive effects had been evaluated in only one review:³⁶ the trend was positive but no significant effect was stated. In 2 of the 8 reviews, there were suggestions of relaxant property, but these conclusions were based on a small number of studies included in the review and had not been based on a meta-analysis.^{6,36}

Antihypertensive effect of *Crocus sativus* was mentioned in 2 reviews.^{36,37} Regarding to antitussive effect of *Crocus sativus*, it is discussed in 3 studies.^{6,36,37} In 2 of 8 reviews, cytotoxic effects of *Crocus sativus* were found.^{39,40} Given the anxiolytic aphrodisiac effects of *Crocus sativus*, it is stated in 3 reviews.^{6,36,37} It is stated that *Crocus sativus* is a remedy for kidney problems.³⁷ One of 8 reviews emphasized on the learning and memory improving properties of *Crocus sativus*.³⁶ Hypnotic, anxiolytic and anesthetic effects of *Crocus sativus* is mentioned in 2 reviews.^{36,37} 2 of 8 reviews were stated effects of *Crocus sativus* on the eyes.^{36,37} 2 of 8 reviews were mentioned effects of *Crocus sativus* on premenstrual symptoms.^{37,38} Antibacterial effects of *Crocus sativus* were discussed in only one review.³⁸ One of the reviews was stated bronchodilatory effect of *Crocus sativus*.³⁷ Effects of *Crocus sativus* on the gastrointestinal tract were stated in two reviews.^{40,41}

DISCUSSION

In spite of wide differences in the reviews including the type of study (animal or human study) and the interventions used, lots of therapeutic effects of *Crocus sativus* have been reported. *Crocus sativus* is confirmed to have positive effect in the treatment of pancreatic, skin, liver, colorectal, breast, cervical cancers and Leukemia via its antioxidant activity.³⁴ However, in another study, it was stated that *Crocus sativus* could be effective in the treatment of liver, spleen, kidney, stomach and uterus cancers with galenic preparation of *Crocus sativus*. It has suggested that *Crocus sativus* can inhibit the process of carcinogenesis effectively¹⁰ and it can act as effective chemo-preventive agent¹⁰ that these results are in harmony with that of another review.³⁸ In the review conducted by Hosseinzadeh, Avicenna mentioned that *Crocus sativus* is used for malignant ulcers of the uterus. However, it is stated that lots of clinical trials are needed to be carried out to prove its effect in vivo.

Regarding anti-tumor effect of *Crocus sativus*, the inhibitory effect of different isolated carotenoid ingredients of *Crocus sativus* on colony formation of human HeLa cells was shown.¹⁰ *Crocus sativus* extract had no effect on two normal human cell lines, but inhibited the growth of all tested human malignant cells in dose-dependent manner. *Crocus sativus* and its main carotenoid constituents are proposed as an alternative in the treatment or prevention of different kinds of tumor as natural antitumor agents.¹⁰ It was shown that *Crocus sativus* extract and its ingredients, i.e. crocin, safranal, picrocrocin, and carotenes inhibited the growth of different types of tumor cell.⁴ Although several hypotheses have been offered so far, the exact mechanism(s) of anticarcinogenic and tumoricidal effects of *Crocus sativus* and its main constituents are not clear.

Crocus sativus extract was shown to have antidepressant effect.³⁷ In a review performed by Moshiri, antidepressant effects of saffron were discussed and it was indicated that *Crocus sativus* extract was effective as an antidepressant drug. In a review,³⁸ it was mentioned that *Crocus sativus* was an exhilarant and acted as a cardiac tonic and was used as an antidepressant drug for a long time. In the countries where it is cultivated (e.g. Iran), *Crocus sativus* tea is well known for improving mood.³⁸ Stigma and petal extracts of *Crocus sativus* and its constituents, safranal and crocin, kaempferol have shown antidepressant activity in the forced swimming test in mice and rats.²¹⁻²⁶ However, more studies with larger population and longer duration are needed to confirm these results. In the Meta-analysis,²¹ it was indicated that *Crocus sativus* can treat to some extent depression in individuals with major depressive disorder (MDD). In this meta-analysis,²¹ the effects of *Crocus sativus* supplementation versus placebo control group was compared and *Crocus sativus* was found to be more effective. However, further studies are required to expand this result.

The anticonvulsant activities of *Crocus sativus* stigma i.e. safranal and crocin were evaluated using pentylenetetrazole (PTZ). Safranal showed anticonvulsant activities while Crocin did not show this effect.³⁷ In another review, anticonvulsant effects of *Crocus sativus* have been reported in both PTZ and maximal electroshock (MES).

The presence of flavonoids, tannins, anthocyanins, alkaloids, and saponins stigma and petal extracts of *Crocus sativus* demonstrated anti-nociceptive and anti-inflammatory activity. The result of this study was in accordance with the review conducted by Wallis.³⁶ In this review, it was

stated that *Crocus sativus* extracts have been traditionally used against fever as well as for pain relief in gingivitis and lumbar pain.⁶ Besides, in another study,⁴³ *Crocus sativus* has been proposed to be used topically to treat inflammation and to decrease the toothache in children. Rouhi and colleagues stated that phenolic compound existing in the aloe vera has anti-inflammatory and anti-microbial effects.⁴³

In another review,³⁷ it was stated that *Crocus sativus* improved vision and prevented related eye diseases. *Crocus sativus* is used for the treatment of day blindness (hemeralopia). Its eyewash property is used to treat eye bruise. Another study confirmed the results of this study and stated that crocin isolated from *Crocus sativus* is able to increase the blood flow in the retina significantly and it can be used to treat retinopathy and age-related macular degeneration.³⁶ However, several studies may help to prove Avicenna's assertion regarding to the application of *Crocus sativus* for eye diseases. Definitive clinical trials are required to confirm the effect of *Crocus sativus* on eye diseases such as hemeralopia.

In a review study, aphrodisiac activity of the *Crocus sativus* aqueous extract, crocin, safranal, sildenafil and saline were evaluated.⁴⁵ The extract and Crocin, at all doses were effective, but not Safranal. In both human and animal studies, safranal and crocin increased sexual behavioral factors such as mounting frequency, intromission frequency and erection frequency.⁴⁵

In a review study,³⁸ it was found that stigma of saffron is useful in the treatment of premenstrual syndrome. It is in line with the review study performed by Rios.⁶ It has been reported that *Crocus sativus* has a uterine sedative property, which is useful in treatment of dysmenorrheal diseases and premenstrual syndrome, but there are reports of its toxicity and at least one death has been reported.

CONCLUSION

This review indicated that despite remarkable differences in interventions, and type of studies carried out on this plant (in vivo and in vitro), it seemed to have many therapeutic effects in the treatment of various types of diseases. In addition, it was illustrated that the overlooking different therapeutic effects of *Crocus sativus* may be valuable to find new biological activities and compounds, as well as to the production of new drugs. This study suggests that *Crocus sativus* and its constituents, such as crocin, crocetin and safranal, may be safe natural alternative against a variety of diseases. However, to be able to use the results of these studies in our daily life, lots of double-blind, randomized, placebo-controlled clinical trials with larger population and longer duration must be carried out and its toxicity and safety in each and every cases of therapeutic effects should be assessed.

CONFLICT OF INTEREST

There is no conflict of interest associated with this study.

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