ISSN 0975-6299 Vol 2/Issue 1/ Jan-Mar 2011

International Journal of Pharma and Bio Sciences

REVIEW ARTICLE

PHARMACOGNOSY

DETAILED PROFILE OF *CROCUS SATIVUS*

Corresponding Author

KATARIYA DHIRAJKUMAR CHAMPALAL

P.D.E.A's Seth Govind Raghunath Sable College of Pharmacy, Saswad,India

Co Authors

NERKAR NILAKSHI [1], GADIYA RAJ VIJAY [2] and ABHYANKAR M. M [1].

[1] P.D.E.A's Seth Govind Raghunath Sable College of Pharmacy, Saswad,India
[2] Research Associate Centaur Pharmaceuticals, Pune,India

ABSTRACT

Crocus sativus L. is an herbaceous perennial-cormous plant which is believed to show many pharmacological actions. The plant contains important constituents like crocetin, picrocrocin, safranal (main component for characteristic aroma). Safranal is the aglycon of picrocrocin; those are responsible for many pharmacological actions. In ayurveda saffron is used to cure chronic diseases such as asthma, arthritis, skin diseases, spasmodic disorders, digestive disorders, digestive disorders, kidney disorders. Saffron is also useful in liver and spleen enlargement. Very few modern preclinical and clinical studies have been performed on the plant. In this review, we have made an attempt to compile some of its important and scientifically proven pharmacological activities.

KEYWORD

Saffron, Crocus sativus, Safranal, Crocetin.

INTRODUCTION

Saffron (*Crocus sativus L*) belongs to the family Iridaceae. It is an herbaceous perennial-cormous plant. The height of the plant is about 0.25 to 0.5 foot and the width is about 0.25 to 0.5 foot. The best season for the growth saffron is early spring. It prefers sunny to part shady, moderately dry, well-drained, ordinary garden soil. The flower styles are commonly used as a flavoring and yellow colouring for various foods such as bread, soups, sauces, rice and puddings .Yields per plant are extremely low, about 4000 stigmas yield 25g of saffron. The corms are toxic to young animals, so this report of edibility should be treated with some caution. [1-15]

In Ayurveda, saffron is used to cure chronic diseases such as asthma and arthritis. It is also useful in treating cold and coughs. Ayurvedic medicines containing saffron are used to treat acne and several skin diseases. A paste of the spice can be used as a dressing for bruises and superficial sores.

Ancient texts on Ayurveda have information about the herb's use as an aphrodisiac. It is a stimulant. It is largely used as an indigenous medicine across India. Saffron enjoys great reputation as a drug which strengthens the functioning of the stomach and promotes its action. It also counteracts spasmodic disorders and sustains involuntary muscle contraction. According to five preliminary double-blind studies, use of saffron at 30 mg daily is more effective than placebo and equally effective as standard treatment for major depression.

Test-tube and animal studies hint that saffron and its constituents may help prevent or treat cancer, reduce cholesterol levels, protect against side effects of the drug cisplatin, and enhance mental function.

It is beneficial in the treatment of several digestive disorders. Its use has been found especially valuable in flatulent colic. It is also used in the fevers, melancholia and enlargement of the liver and spleen. It is used in medicines that reduce inflammation. A combination of saffron and ghee is used to treat diabetes. Saffron also merits usage in disorders of Brain. It has been found beneficial in the treatment of kidney disorders. It acts as a diuretic, if soaked overnight in water and administered with honey. [16-22]

TAXONOMY

Saffron belongs to the family Iridaceae of the order asparagales. The class is liliopsida under the division Magnoliophyta. Taxonomy of *Crocus sativus* is shown in Table no : 1

Table no: 1
Taxonomy of Crocus sativus.

Scientific classification		Subfamilies and tribes
Kingdom:	Plantae	• **Subfamily-** Crocoideae • **Subfamily-** Iridoideae o Tribe- Irideae o Tribe- Mariceae o Tribe- Sisyrinchieae o Tribe- Tigridieae • **Subfamily** -Isophysidoideae • **Subfamily -**Ixioideae o Tribe -Ixieae o Tribe- Pillansieae o Tribe -Watsonieae • **Subfamily-** Nivenioideae
Division:	Magnoliophyta	
Class:	Liliopsida	
Order:	Asparagales	
Family:	Iridaceae	
Genus:	*Crocus*	
Species:	***C. sativus***	

Saffron is a small perennial plant. Gray-green leaves have hairy margins and grow to about 1 or1-1/2 feet long. About August or September, the corm produces a funnel-shaped, reddish-purple (sometimes lilac or white) flower. The flowers are hermaphrodite (has both male and female organs) and are pollinated by Bees, butterflies. The flower has three stigmas, which are the distal ends of the plant's carpels. Together with its style, the stalk connecting the stigmas to the rest of the plant and is a sterile triploid mutant. [23]

PHYTOCHEMISTRY [24-28, 58]

Saffron contains more than 150 volatile and aroma-yielding compounds. It also has many nonvolatile active components, many of which are carotenoids, including zeaxanthin, lycopene, and various α- and β-carotenes.[47]

Saffron has golden yellow-orange colour is primarily the result of α-crocin. This crocin is trans-crocetin di-(β-D-gentiobiosyl) ester (systematic (IUPAC) name: 8,8-diapo-8,8-carotenoic acid). Its formula is $C_{44}H_{70}O_{28}$. [14]

Crocin with weak bases it is converted into *crocetin* ($C_{34}H_{46}O_9$), peculiar sugar not quite identical with dextrose, hence called *crocose*.

The resultant α-crocin is a carotenoid pigment that may comprise more than 10% of dry saffron's mass [14, 15]. A second element underlying saffron's aroma is 2-hydroxy-4,4,6-trimethyl-2,5-cyclohexadien-1-one, the scent of which has been described as "saffron, dried hay like".

The flavouring property of saffron is due to the bitter glycoside picrocrocin chemically it is 4-(β-D- glucopyranosyloxy)- 2, 6, 6-trimethylcyclohex- 1- ene- 1- carboxaldehude. (chemical formula- $C_{16}H_{26}O_7$). Safranal is less bitter than picrocrocin and may comprise up to 70% of dry saffron's volatile fraction in some samples.[24, 26]. It gives saffron much of its distinctive aroma. When saffron is dried after its harvest, the heat, combined with enzymatic action, splits picrocrocin to yield D-glucose and a free safranal molecule [5]. Dry saffron is highly sensitive to fluctuating pH levels, and rapidly breaks down chemically in the presence of light and oxidizing agents. Analysis of Saffron is shown in Table No. 2

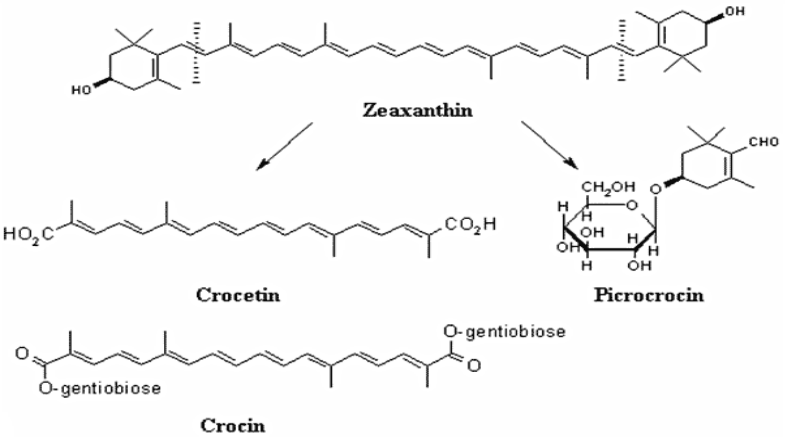
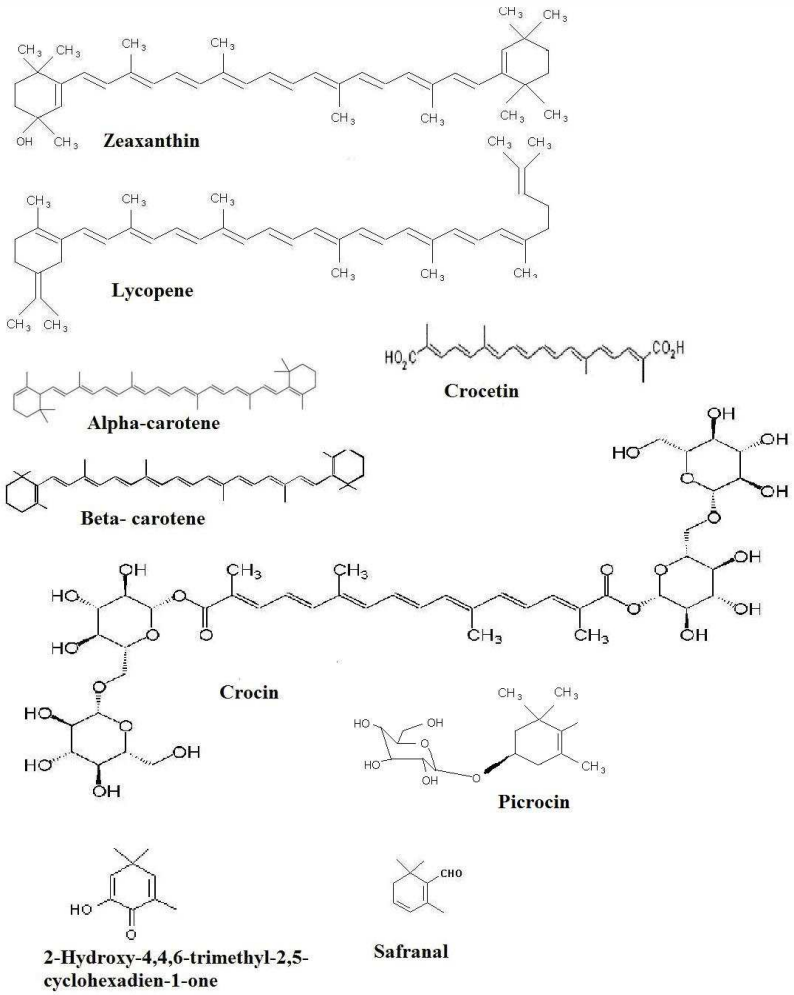


Table no: 2
Analysis of Saffron [27]

Proximate analysis of saffron		Proximate analysis of saffron	
Component	Mass %	Component	Mass %
Water-soluble components	53.0	**Lipids**	12.0
→ Gums	10.0	→ Non-volatile oils	6.0
→ Pentosans	8.0	→ Volatile oils	1.0
→ Pectins	6.0	**Protein**	12.0
→ Starch	6.0	**Inorganic matter ("ash")**	6.0
→ α–Crocin	2.0	→ HCl-soluble ash	0.5
→ Other carotenoids	1.0	Water	10.0
Fiber (crude)	5.0		



PHARMACOLOGY

Saffron has been traditionally used as an Bitter, acrid, fragrant, stimulent, tonic, stomachic, aphrodisiac, anodyne, antispasmodic, emmenagogue, diauretic, anticancer laxative, galactogogue and are useful in bronchitis, pharyngopathy, cephalgia, vomiting, fever, melancholia, hepatomegaly, vitiated conditions Kapha, epilepsy, inflamations, and skin diseases.[29]

1) ***Anticonvulsant activity:-*** The effects of aqueous and alcoholic extract of Crocus sativus L. stigmas (CSS) were studied in mice. Crocetin is mainly responsible for the above pharmacological activities.[22] Three anticonvulsant evaluation tests, namely the Pentylenetetrazole (PTZ) seizure test, Maximal electroshock seizure test (MES) and Maximum non-fatal dose and acute toxicity**.** The ethanolic and aqueous extracts increased the latency of convulsions induced by PTZ dose-dependently, but failed to produce complete protection against mortality. Neither extracts had seizure-protective effects in the MES test. CSS delayed the onset of tonic convulsions, but failed to produce complete protection against mortality. In the MES test, both extracts decreased the duration of tonic seizures. [30, 31]
2) ***Anticancer activity:-*** Saffron and its characteristic components possess anticarcinogenic and antitumor activities *in vivo* and *in vitro*. [32] It was shown that saffron extract and its purified characteristic compounds crocin, safranal, picrocrocin, and ß-carotene inhibited different types of tumor cell growth [33-39]. It was reported that

a novel glucoconjugate isolated from corms and callus of saffron possessed cytotoxic activity against different tumor cells [40-44]. Glucoconjugate from corms of *Crocus sativus L.* possessed cytotoxic activity on human tumor cells derived from fibrosarcoma, cervical epithelioid carcinoma, and breast carcinoma. [45, 46]. Oral administration of saffron extract induced a dose-dependent inhibition of the growth in mice of ascite tumors [38, 48-53].

3) ***Antinociceptive activity :-*** The effects of aqueous and ethanolic maceration extract of *Crocus sativus* L. stigmas (CSS) and petals were studied in mice. The antinociceptive effects of the extracts may be due to their content of flavonoids, tannins, anthocyanins, alkaloids and saponins. Antinociceptive activity was examined using the hot plate and writhing tests. In hot plate test, aqueous and ethanolic petal extracts showed no significant antinociceptive activity but it exhibit antinociceptive activity against acetic acid induced writhing. It is concluded that saffron stigma and petal aqueous and ethanolic maceration extracts shows antinociceptive effects in chemical pain tests. [54, 55]
4) ***Anti-inflammatory effect : -*** The effects of aqueous and ethanolic maceration extract of *Crocus sativus* L. stigmas (CSS) and petals were studied in mice. The anti-inflammatory effects of the extracts may be due to their content of flavonoids, tannins, anthocyanins, alkaloids and saponins. Only the stigma extracts showed weak to moderate effect against acute inflammation. In chronic inflammation, both aqueous and ethanolic stigma extracts, as well as ethanolic petal extract, exerted anti-inflammatory effects but aqueous petal extract did not exhibit significant anti-inflammatory activity. In higher doses, the aqueous and ethanolic extracts of stigma showed significant activity against the acute inflammation. It is concluded that saffron stigma and petal aqueous and ethanolic maceration extracts shows acute and/or chronic anti-inflammatory activity. [54-56]
5) ***Anti-depressant :-*** A number of recent preclinical and clinical studies indicate that stigma and petal of *Crocus sativus* have antidepressant effect. The clinical findings suggest that saffron is a safe and effective antidepressant. [27, 57, 59]
6) ***Relaxant activity :-*** The effects of aqueous ethanolic extract of *Crocus sativus* were studied on the tracheal chains of guinea–pigs for its relaxant activity. The relaxant effect of the extract may be due to the safranal present in the *Crocus sativus*. The results indicated that safranal was, at least in part, responsible for the relaxant effect of *Crocus sativus*. [60, 61]
7) ***Antihypertensive activity:-*** The effect of aqueous and ethanol extracts of *Crocus sativus* petals is done on the isolated rat vas deferens and guinea-pig ileum induced by Electrical field stimulation (EFS) for their antihypertensive activity. Aqueous and ethanol extracts of *Crocus sativus* petals reduced the blood pressure in a dose-dependent manner. [61]
8) ***Antioxidant activity:-*** The effects of aqueous and methanol extract of *Crocus sativus* L. stigmas (CSS) were studied for examination of in vitro antioxidant properties and its effect on Abeta (1-40) fibrillogenesis. The water: methanol (50:50, v/v) extract of *Crocus sativus* stigmas possesses good antioxidant properties. The main carotenoid constituent, trans-crocin-4, the digentibiosyl ester of crocetin, inhibited Abeta fibrillogenesis at lower concentrations than dimethylcrocetin, revealing that the action of the carotenoid is enhanced by the presence of the sugars. *Crocus sativus* stigma constituents for inhibition of aggregation and deposition of Abeta in the human brain. [62]
9) ***Antitussive activity :-*** The antitussive activity of *Crocus sativus* stigma and petal extracts and its components, safranal and crocin, was evaluated using the nebolized solution of citric acid 20% in guinea pigs.

The ethanolic extract of saffron and safranal reduced the number of cough. The ethanolic and aq. extracts of petal and crocin did not show antitussive activity. [63]

10) ***Antihyperlipidemic activity :-***The antihyperlipidemic of *Crocus sativus* were studied on the rats. The antihyperlipidemic effect is due to the crocin present in the *crocus sativus*. [64, 65]

11) ***Defense against oxygen toxicity:-*** In this investigation used methods were compared for the measurement of superoxide dismutase activity in *Crocus sativus* corm extract. The methods, based on a competition between the enzyme itself and another superoxide scavenger, involved respectively cytochrome c reduction, nitro blue tetrazolium reduction, and pyrogallol autoxidation. [66]

12) ***Effect in improving ocular blood flow and retinal function:*** - The effect of *Crocus sativus* in improving ocular blood flow and retinal function is done by the studying the effect on the vasodilation. Crocin analogs isolated from *Crocus sativus* L. were found to significantly increase the blood flow in the retina and choroids and to facilitate retinal function recovery. These results indicated that crocin analogs could be used to treat ischemic retinopathy and/or age-related macular degeneration. [67]

13) ***Inhibitory effect on Platelet aggregation :-*** The inhibitory activity of saffron extract was studied on human platelets. Platelet aggregation and lipid peroxidation were evaluated with platelet rich plasma (PRP) and platelet membranes respectively. The results indicate that the aqueous extract of saffron may have component(s), which protect platelets from aggregation and lipid peroxidation. [68]

14) ***Radical scavenging activity_:-*** Radical scavenging activity is involved in aging processes, anti-inflammatory, anticancer and wound healing activity. Hence, in the present study the DPPH radical scavenging activity of a natural product that possesses biological properties, an extract of saffron, and some of its bioactive constituents (crocin, safranal) was studied. It was shown that a methanol extract of saffron exhibited high antioxidant activity, although it contains several active and inactive constituents due to the ability to donate a hydrogen atom to the DPPH radical. [69]

15) ***Antityrosinase activity :-*** A common flavonol, kaempferol isolated from the fresh flower petals of *Crocus sativus* was found to inhibit the oxidation of L-3, 4-dihydroxyphenylalanin (L-DOPA) catalysed by mushroom tyrosinase with an ID (50) of 67microgram/ml (0.23mM). [13, 70-73].

16) *Apoptosis effects:-*

An apoptosis effect is mainly due to the crocin present in saffron. Crocin suppresses the effect of tumor necrosis factor (TNF)-alpha on neuronally differentiated PC12 cells. In result the crocin inhibits neuronal cell death induced by both internal and external apoptotic stimuli. [13, 74]

17) *Catalase activity:-* Catalase activity is shown by crude extract prepared from Saffron corms. Thermostability studies suggested the presence of three isoenzymes with transition temperature of 30^0C, 45^0C and 60^0C, respectively. Thus it appeared that at least three isoenzyme of catalase were *present in dormant saffron corms. [13, 75]*

18) Enzymatic activity:- Three L-lactate dehydrogenase isoenzymes were detected in saffron corms, using potassium ferricyanide as the electron acceptor. Their pH optima were 5.5, 7.5 and 9.5, respectively. All three dehydrogenase were substrate-inhibited by ferricyanide, but at different concentrations; maximum enzymatic activity was observed for 250, 100 and 600 microM ferricyanide, at pH 5.5, 7.5 and 9.5, respectively. Catalytic efficiency, calculated per mg corm extract protein, was 1.9, 1.0 and 0.4 min(-1), respectively at pH 5.5, 7.5 and 9.5, Pseudo first order rate constant was also different under the three pH conditions. Malate was

an inhibitor for the isoenzyme active at pH 9.5, but had no effect on the others. [13, 75]

19) ***Effect on Uterus and Estrus Cycle :-*** *Crocus sativus* has hot and dry qualities, stimulant or inebriant depending on dosage, sun dried filaments ingested strengthen the uterus and treats menstrual problems, stimulates sexual desires for women. [13, 76]

20) ***Glutathione S-transferase (GST) activity :-*** The treatment of mice with aq. extract of saffron can significantly inhibit genotoxicity produce by cisplatin, cyclophosphamide, mitomycin and urethane. These genotoxins alone can inhibit glutathione S-transferase (GST) activity. It was also observes that saffron pretreatment attenuated the inhibitory effects of genotoxins on GST activity. [13, 77, 78]

21) ***Immunomodulating activity :-*** The Immunomodulating effect of saffron was due to proteoglucan which is present in it. This proteoglycan is highly cytotoxic on human tumor cells. [13, 79]

22) ***Modulatory effects :-*** In mice, an effect of *Crocus sativus* stigmas partially prevented the decreases in body weight, hemoglobin levels and leucocyte count. Treatment with saffron extract also significantly prolonged the life span of cisplatin-treated mice almost three-fold. [13, 77, 80]

TOXICOLOGY [81]

In respect to LD_{50} values and maximum non-fatal doses, the stigma extracts were more toxic than the petal extracts. LD_{50} values of aqueous and ethanolic stigma extracts have been reported as 1.6 g/kg, i.p. (1.16, 2.22) and 3.38 g/kg, i.p. (2.55, 4.52) in mice [83]. According to a toxicity classification, stigma and petal extracts are "relatively toxic" and "low toxic", respectively. Treatment with the *Crocus sativus* extract also significantly prolonged the life span of cisplatin-treated mice almost three-fold [46, 82]. Toxicity studies showed that the hematological and biochemical parameters were within normal range with saffron extract. The maximum non-fatal doses of stigma aqueous and ethanolic extracts were 0.8 g/kg and 2 g/kg (i.p.), respectively and of petal extract were 3.6 g/kg and 8 g/kg (i.p.), respectively [81].

REFERENCES

1. Hedrick. U. P. Sturtevant's Edible Plants of the World. Dover Publications, ISBN 0-486-20459-6, (1972).
2. Grieve. A, Modern Herbal. Penguin, ISBN 0-14-046-440-9, (1984).
3. Chiej. R. Encyclopaedia of Medicinal Plants. MacDonald, ISBN 0-356-10541-5, (1984).
4. Holtom. J. and Hylton. W. Complete Guide to Herbs. Rodale Press, ISBN 0-87857-262-7, (1979).
5. Lust. J. The Herb Book. Bantam books, ISBN 0-553-23827-2, (1983).
6. Harrison. S. Wallis. M. Masefield. G. The Oxford Book of Food Plants. Oxford University Press, (1975).
7. Facciola. S. Cornucopia - A Source Book of Edible Plants. Kampong Publications, ISBN 0-9628087-0-9, (1990).
8. Phillips. R. & Foy. N. Herbs Pan Books Ltd. London, ISBN 0-330-30725-8, (1990).
9. The Plantsman, Royal Horticultural Society, Vol. 9. (1986 – 1987).
10. Hill. A. F. Economic Botany. The Maple Press, (1952).
11. Polunin. O. and Huxley. A. Flowers of the Mediterranean. Hogarth Press, ISBN 0-7012-0784-1, (1987).
12. Bown. D. Encyclopaedia of Herbs and their Uses. Dorling Kindersley, London, ISBN 0-7513-020-31, (1995).
13. Nandan Kumar Jha, Pytopharm, Crocus sativus Feature, Article: 3-12, (2005).
14. Duke. J. A. and Ayensu. E. S. Medicinal Plants of China Reference Publications, Inc. 1985 ISBN 0-917256-20-4.
15. Ben Frik, Wyk Michael wink, Medicinal plants of the world, 3rd edition: 116, (2003).

16. Kirtikar and Basu , Indian medical plants, 2 nd edition, Vol 4th : 2463, (1993).
17. Arya Vaidya, Indian medical plants, a compendium of 500 species, Volume 2: 212.
18. Akhondzadeh S, Tahmacebin Pour N, Noorbala A A, et al. Crocus sativus L. in the treatment of mild to moderate depression: a double-blind, randomized and placebo-controlled trial, Phytother Res. Volume: 19:148–51, (2005).
19. Noorbala A A, Akhondzadeh S, Tahmacebi-Pour N, et al. Hydro-alcoholic extract of Crocus sativus L. versus fluoxetine in the treatment of mild to moderate depression: a double-blind, randomized pilot trial. J Ethnopharmacol, Vol: 97:281–4, (2005).
20. Akhondzadeh S, Fallah-Pour H, Afkham K, et al. Comparison of Crocus sativus L. and imipramine in the treatment of mild to moderate depression: a pilot double-blind randomized trial, BMCComplement Altern Med. Vol 4:12, (2004).
21. Moshiri E, Basti AA, Noorbala AA et al. Crocus sativus L. (petal) in the treatment of mild-to-moderate depression: A double-blind, randomized and placebo-controlled trial. Phytomedicine, Vol Sept, (2006)
22. Akhondzadeh Basti A, Moshiri E, Noorbala AA, et al. Comparison of petal of Crocus sativus L and fluoxetine in the treatment of depressed outpatients: a pilot double-blind randomized trial. Prog Neuropsychopharmacol Biol Psychiatry. Vol Dec, (2006).
23. Peter Goldblatt, Ph.D - Phylogeny and classification of Iridaceae. Ann. Missouri Bot. Gard. Vol 77: 607–627, (1990).
24. McGee, H On Food and Cooking: The Science and Lore of the Kitchen, Scribner, ISBN 0-684-80001-2 , (2004).
25. Katzer, G, Saffron Crocus sativus L.", Gernot Katzer's Spice Pages, Vol: Jan, (2001).
26. Deo, B, "Growing Saffron – The World's Most Expensive Spice", Crop & Food Research (New Zealand Institute for Crop & Food Research) (Vol 20) (2003).
27. Dharmananda, S, "Saffron: An Anti-Depressant Herb", Institute for Traditional Medicine, (2005)
28. Goyns, MH, Saffron, Taylor & Francis, ISBN 90-5702-394-6, (1999).
29. Indian medical plants, a companium of 500 species, Volume 2, Arya Vaidya Sala: 212.
30. Abe K, Saito H. Effects of saffron extract and its constituent crocin on learning behavior and long-term potentiation. Phytother Res. Vol 14:149-52. (2000).
31. Vida JA, Foye WO, Lemke TL, Williams DA, eds. Principles of Medicinal Chemistry. London: Williams and Wilkins; 1995.
32. Cancer Lett. Feb 27, Vol:100: 23-30, (1996).
33. Garcia-Olmo DC, Riese HH, Escribano J, Ontañon J, Fernandez JA, Atienzar M, Garcia-Olmo D. Effects of long-term treatment of colon adenocarcinoma with crocin, a carotenoid from saffron (Crocus sativus L.): an experimental study in the rats. Nutr. Cancer Vol: 35(2): 120–126, (1999).
34. Abdullaev FI, Gonzalez de Mejia E. Inhibition of colony formation of Hela cells by naturally occurring and synthetic agents, BioFactors, Vol: 5(3):133–138, (1995-96).
35. Morjani H, Tarantilis P, Polissiou M, Manfait M. Growth inhibition and induction of crythroid differentiation activity by crocin, dimethylcrocetine and ß-carotene on K562 tumor cells, Anticancer Res, Vol 10: 1398–1406, (1990).
36. Tarantilis PA, Morjani H, Polissiou M, Manfait M. Inhibition of growth and induction of differentiation promyelocytic leukemia (HL-60) by carotenoids from Crocus sativus L, Anticancer Res, Vol: 14(5A):1913–1918, (1994)
37. Nair S.C, Kurumboor S.K, Hasegawa J.H, Saffron chemoprevention in biology and medicine: a review, Cancer Biother, Vol 10(4):257–264, (1995).
38. Nair S C, Pannikar B, Pannikar K R, Antitumour activity of saffron (Crocus sativus), Cancer Lett, Vol 57(2):109–114, (1991).
39. Abdullaev F I, Frenkel G D. Effect of saffron

on cell colony formation and cellular nucleic acid and protein synthesis, Bio Factors, Vol: 3(3): 43-45, 201–204, (1992).

40. Escribano J, Rios J, Fernandez JA. Isolation and cytotoxic properties of novel glycoconjugate from corms of saffron plant (Crocus sativus L.), Biochim Biophys Acta, Vol: 1426 (1) : 217–222, (1999).
41. Escribano J, Diaz-Guerra MJ, Riese H H, Ontanon J, Garcia-Olmo D, Garcia-Olmo DC, Rubio A, Fernandez JA, In vitro activation of macrophages from corms of Crocus sativus L, Cancer Lett, vol 144(1):107–114, (1999).
42. Escribano J, Piqueras A, Medina J, Rubio A, Alvarez-Orti M, Fernandez JA, Production of a cytotoxic proteoglycan using callus culture of saffron corms (Crocus sativus L.), J Biotechnol, Vol 73(1):53–59, (1999).
43. Escribano J, Diaz-Guerra M J, Riese H H, Alvarez A, Proenza R, Fernandez J A, The cytotoxic effect of glucoconjugate extracted from corms of saffron plant (Crocus sativus) on human cell lines in culture, Planta Med 66(2):157–162, (2000).
44. Fernandez J A, Escribano J, Piqueras A, Medina J. A glycoconjugate from corms of saffron plant (Crocus sativus L.) inhibits root growth and affects in vitro cell viability, J Exp Bot, Vol 51:731–737, (2000).
45. Fernandez J A, Escribano J, Piqueras A, Medina J. A glycoconjugate from corms of saffron plant (Crocus sativus L.) inhibits root growth and affects in vitro cell, Sci Congr, Vol 3:125–126, (1990).
46. Nair S C, Salomi M J, Panikkar B, Pannikkar K R, Modulatory effects of Crocus-sativus and Nigella-sativa extracts on cisplatin-induced toxicity in mice, J Ethnopharmacol, Vol **5**: 67–84, (1991).
47. Phytochemical methods, A guide to modern techniques of plant analysis, J. B. Harborne, Third edition: 139, (1998)
48. Abdullaev Jafarova F, Caballero-Ortega H, Riveron-Negrete L, et al. In vitro evaluation of the chemopreventive potential of saffron, Rev Invest Clin, Vol 54: 430–6, (2003).
49. Escribano J, Alonso G L, Coca-Prados M, et al. Crocin, safranal and picrocrocin from saffron (Crocus sativus L.) inhibit the growth of human cancer cells in vitro, Cancer Lett; Vol 100:23–30, (1996)
50. Abdullaev F I, Espinosa-Aguirre J J, Biomedical properties of saffron and its potential use in cancer therapy and chemoprevention trials, Cancer Detect Prev, Vol 28: 426–32, (2004).
51. Molnar J, Szabo D, Pusztai R, et al. Membrane associated antitumor effects of crocine-, ginsenoside- and cannabinoid derivates. Anticancer Res, Vol: 20: 861–7, (2000).
52. Abdullaev F I, Riveron-Negrete L, Caballero-Ortega H, et al. Use of in vitro assays to assess the potential antigenotoxic and cytotoxic effects of saffron (Crocus sativus L.), Toxicol In Vitro, Vol 17:731–6, (2003).
53. Garcia-Olmo D C, Riese H H, Escribano J, et al. Effects of long-term treatment of colon adenocarcinoma with crocin, a carotenoid from saffron (Crocus sativus L.): an experimental study in the rat, Nutr Cancer, Vol: 35:120–6, (2000).
54. Hosseinzadeh H, Ramezani M, Salmani G A. Antinociceptive, anti-inflammatory, J Ethnopharmacol, Vol 73:379–385, (2000).
55. Saxena R S, Gupta B, Saxena K K, Singh R C, Prasad D N, Study of anti-inflammatory activity, Indian medicinal plant. J Ethnopharmacol, Vol 11:319–330, (1984).
56. Ma S, Zhou S, Shu B, Zhou J. Pharmacological studies on Crocus glycosides I. Effects on antiinflammatory and immune function. Zhongcaoyao, Vol 29: 536–539, (1998).
57. Akhondzadeh S, et al., Crocus sativus in the treatment of mild to moderate depression: a double-blind, randomized and placebo-controlled trial, Phytotherapy Research, Vol 19(2):148-151, (2005).
58. Medical natural products, A biosynthetic approach, Second edition, Paul M. Dewick:

231.
59. Prog Neuropsychopharmacol Biol Psychiatry, (2006).
60. J Pharma Pharmacol, Vol 58(10):1385-90, (2006).
61. J. Ethnopharmacol. Vol 84(2-3): 199-203, (2003).
62. J Agric Food Chem, Vol54(23): 8762, (2006).
63. Fitoterapia. Epub, Vol 77(6): 446-8, (2006)
64. Xu GL, Yu SQ, Gong ZN, et al. Study of the effect of crocin on rat experimental hyperlipemia and the underlying mechanisms, Zhongguo Zhong Yao Za Zhi, Vol 30:369–72, (2005).
65. Eur J Pharmacol, Vol 543(1-3): 116-22, (2006)
66. Prikl Biokhim Mikrobiol, Vol 42(1): 111-6, (2006).
67. J Ocul Pharmacol Ther, Vol: 15(2):143-52, (1999).
68. Mol Cell Biochem, Vol 278(1-2): 59-63, (2005).
69. Phytother Res, Vol 19(11): 997-1000, (2005).
70. J Nat Prod, Vol 67(3): 437-40, (2004).
71. J Argic Food Chem, Vol 47(10): 4121-5, (1999).
72. J Nat Prod, Vol 65(10): 1452-6, (2002).
73. Chem. Pharm Bull (Tokyo), Vol 50(10):1305-9, (2002).
74. Life Science, Vol 69(24): 2887-98, (2001).
75. Mol Biol Rep, Vol 29(1-2):125-8, 163-6, (2002).
76. Yao Xue Xue Bao, Vol 11: 94-100, (1964).
77. Daly E S. Protective effect of cysteine and vitamin E, Crocus sativus and Nigella sativa extracts on cisplatin-induced toxicity in rats, J Pharm Belg, Vol 53: 87–93, (1998).
78. Drug Chem Toxicol, Vol 24(4): 421-8, (2001).
79. Cancer Lett, Vol 144(1): 107-14, (1999).
80. J Ethnopharmacol, Vol 31(1):75-83, (1991).
81. Hossein Hosseinzadeh and Hani M Younesi, Antinociceptive and anti-inflammatory effects of Crocus sativus L. stigma and petal extracts in mice. BMC Pharmacol, Vol 2: 7, (2002).
82. Loomis, T A, Essential of Toxicology. Philladelphia, Lea and Febiger. :67–78, (1968).
83. Hosseinzadeh, H.; Khosravan V, Anticonvulsant effect of Crocus sativus L. stigmas aqueous and ethanolic extracts in mice, Arch Irn Med, (2001).