Biological Properties and Medicinal Use of Saffron (*Crocus sativus* L.)

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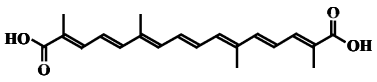
Abstract

From ancient times, the saffron *Crocus sativus* L. is widely used as drug to promote health and fight disease, especially in the Middle East and Southeast Asia. Saffron is cultivated in different parts of the world, but currently mainly in Iran. In view of its wide range of medical uses, the saffron has under gone extensive phytochemical and biochemical studies and variety of biologically active ingredients isolated. Characteristic components of saffron are crocin – responsible of the colour, picrocrocin – responsible of the bitter taste and safranal – responsible odour and aroma. Saffron is non toxic in animal studies (LD_{50} – 20,7 g/kg), non cytotoxic in vitro studies (LD_{50} – 200mkg/ml). During the last decade from different laboratories of the world were reported data on the effect of saffron on coronary artery diseases; on learning behaviour; on ocular blood flow and retinal function; on blood pressure; on contraceptive, anti-inflammatory and antiatherosclerosis activities; antigenotoxic and cytotoxic activities. The goal of this presentation is to summarise and discuss the scientific data on biomedical properties of saffron and main its ingredients, especially on anticancer and antitumor activities. It should be borne in mind that health benefits of saffron may be also from additive and synergistic combinations of phytochemicals. With natural agents, such as saffron, the hope is that their availability, lack of obvious toxicity at effective dose and ability to act against different human health conditions by various mechanism, will be allow their introduction as potential medical drug in clinical trials

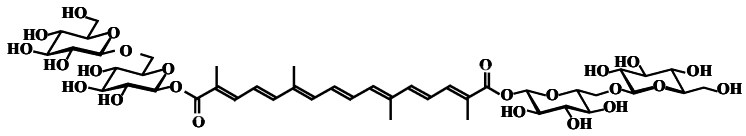
INTRODUCTION

The scientific name for saffron is *Crocus sativus* L. and belongs to the family of Iridaceas, the line of liliaceas. Among the 85 species belonging to the *Crocus* genus, saffron is the most fascinating and intriguing species. The word "saffron" is derived from the Arabic word za'faran, which translates to "yellow." Commercial saffron is made from the dried stigmas of the saffron flower, a triploid sterile plant and has a unique and distinctively pungent, honey-like flavour and aroma. Existed different theories concerning the origin and spread of the saffron. Some of scientists believe that the saffron plant is native to the Orient, other in Greece. No other flower has a more venerable documented history than saffron crocus. Saffron crocus is mainly cultivated in several countries of mild and dry climate. World-wide, 190 tons of saffron are produced each year, for a total of about $190 million (Table 1).

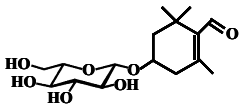
The saffron stigma has a distinct and unique color, flavor and smell and some of the groups of chemical compounds responsible for this:
Color: principal coloring pigments is crocin.
Smell: The main aroma factor in saffron is safranal
Flavor: The special "bitter" flavor is the glycoside picrocrocin..
Molecular structures of the four most important carotenoid secondary metabolites of saffron.



Crocetin



Crocin



Picrocrocin

Safranal

Saffron was more active with parental administration than with oral. Oral administration may be improved by liposome encapsulation of the drug. Liposome encapsulation of saffron produced significant inhibitory effect on the growth of transplanted tumor cells in mice. Animal studies have found that oral administration 100 mg/kg body wt of saffron was more effective against soft tissue sarcomas in mice (Nadkarni, 1976).

Usually saffron recognazed as a safe natural spice. The toxicity of saffron has been found to be quite low. The oral LD_{50} of saffron was 20, 7 g/kg administrated as a decoction. The oral administration of saffron extract at concentrations from 0.1 to 5 g/kg was non-toxic in mice (Abdullaev, 2002).

MEDICINAL AND PHARMACEPTICAL PROPERTIES

Effect on Learning Behavior and Long-term Potentiation

The saffron extract and two of its main ingredients crocin and crocetin, improved memory and learning skills in ethanol-induced learning behavior impairments in mice and rats. Oral administration of saffron may be useful as treatment for neurodegenerative disorders and related memory impairment. (Abe and Saito, 2000; Abe., 1994; Sigura et al., 1995).

Effects on Ocular Blood Flow and Retinal Function

Crocin analogs isolated from saffron significantly increased the blood flow in the retina and choroid as well as facilitated retinal function recovery and it could be used to treat ischemic retinopathy and/or age-related macular degeneration (Xuan et al., 1999).

Effect on Coronary Artery Disease

Fifty milligrams of saffron dissolved in 100ml of milk was administered twice a day to human subjects and the significant decrease in lipoprotein oxidation susceptibility

in patients with coronary artery disease (CAD) indicates the potential of saffron as an antioxidant (Verma and Bordia, 1998).

Effect on Blood Pressure

Aqueous and ethanol extracts of saffron reduced the blood pressure in a dose dependent manner. EFS of the isolated rat vas deferens also were decreased by these saffron extracts (Fatehi, 2003).

Antinociceptive and Anti-inflammatory Effects

Saffron stigma and petal extracts exhibited antinociceptive effects in chemical pain test as well as acute and/or chronic anti-inflammatory activity and these effects might be due to their content of flavonoids, tannins, anthocyanins, alkaloids, and saponins (Hosseinzadeh and Yiounesi, 2002).

Antidepression Effect

In clinical trial have demonstrated that saffron may be of therapeutic benefit in the treatment of mild to moderate depression (Akhondzadeh, 2004; Noorbala, 2005).

Anticonvulsant Effect

In Iranian traditional medicine, the saffron had been used as an anticonvulsant remedy. In experiments with mice using maximal electroshock seizure (MES) and pentylenetetrazole (PTZ) tests have demonstrated that the aqueous and ethanolic extracts of saffron possess anticonvulsant activity. (Hosseinzadeh and Khosrava, 2002).

Antiparkinsonian Effect

Crocetin, which is an important ingredient of saffron may be helpful in preventing Perkinsonism (Ahmad, 2005)

Antiatherosclerosis Effect

Recently it was demonstrated that suppression of LDL oxidation by crocetin contributes to the attenuation of atherosclerosis.

Mutagenic or Antimutagenic Effects

It was reported that crocin and dimethyl-crocetin isolated from saffron were non-mutagenic (Salomi, 1991). Using the Ames/Salmonella test system (strains TA97; TA98; TA100; TA102, and TA1538), we demonstrated that the saffron extract itself in concentration up to 1500 mg/plate was non-toxic, non-mutagenic, and nonantimutagenic (Abdullaev, 2002, 2003).

A test compound was considered mutagenic if the number of the His^+ revertant colonies was increased at least twice over the value of the corresponding control (MI > 2), over at least three doses levels, and a reproducible dose-response curve could be demonstrated.

Antigenotoxic Effect

The topical administration of saffron extracts (100 mg/kg body weight) inhibited the initiation/promotion of 7,12-dimethylbenz [a] anthracene (DMBA)-induced skin tumors in mice. The oral administration of the same dose of saffron extracts restricted tumor incidence of 20-methylcholanthrene (MCA)-induced soft

tissue sarcomas in mice (Salomi, 1991). Extracts from saffron stigmas prolonged the life span of cisplatin-treated mice (Nair, 1991, 1993, 1994). Pretreatment with the aqueous extract of saffron in experiments with Swiss albino mice significantly inhibited the genotoxicity of cisplatin, cyclophosphamide, mitomycin, and urethane (Prekumar, 2001, 2003). Crocetin from saffron also ameliorates bladder toxicity of the anticancer agent cyclophosphamide without altering its antitumor activity (Nair, 1993). The treatment of animals with cysteine (20 mg/kg body weight) together with saffron extract (50 mg/kg body weight) significantly reduced the toxic effects caused by cisplatin (Daly, 1998).

Tumoricidal Effect

The oral administration of the saffron extract increased the life span of Swiss albino mice intraperitoneally transplanted with sarcoma-180 (S-180) cells, Ehrlich ascites carcinoma (EAC) and Dalton's lymphoma ascites (DLA) tumors (Nair, 1991). In an animal model (frog embryos), crocetin, from saffron was effective in treating certain types of cancer (Martin, 2002). The long-term treatment with crocin significantly increased survival time and decreased tumor growth rate, induced by rat adenocarcinoma DHD/K12-PROb cells (Garcia-Olmo, 1999). An increase in the levels of b-carotene and Vitamin A in the serum of laboratory animals under oral administration of saffron extracts was detected and suggested that saffron carotenoids possessed provitamin A activity according to the hypothesis that the action of carotenoids was dependent upon its conversion to retinal (Vitamin A), because most of the evidence supporting the anticancer effects of carotenoids were referred to b-carotene (Daly, 1998, Tarantilis, 1994).

Cytotoxic Effect

The ethanolic saffron extract significantly inhibited the colony formation and cellular DNA and RNA synthesis, whereas inhibition of protein synthesis was not detected. Crocetin, from saffron inhibited intracellular nucleic acid and protein synthesis in malignant human cell lines and no had effect on colony formation. The inhibition of growth of human chronic myelogenous leukaemia K562 and promyelocytic leukaemia HL-60 cells by dimethyl-crocetin, crocetin, and crocin with 50 % inhibition (ID50) reached at concentrations of 0.8 and 2 mM, respectively, (Morjani,1990; Tarantilis,1994). Cytotoxicity of dimethylcrocetin and crocin to various tumors cell lines (DLA, EAC, S-180, L1210 leukemia, and P388 leukemia) and to human primary cells from surgical specimens (osteosarcoma, fibrosarcoma, and ovarian carcinoma) was detected (Nair, 1995). The inhibitory effect of the ethanolic saffron extract on the in vitro growth of HeLa cells (ID50 = 2.3 mg/ml) was mainly due to crocin (ID_{50} of 3 mM) (Escribano, 1996).

Proposed Mechanisms for Cancer Preventive and Tumoricidal Effects of Saffron

Different hypotheses for the modes of anticarcinogenic and antitumor actions of saffron and its components have been proposed (Abdullaev, 2002, 2004).

1. The inhibitory effect on cellular DNA and RNA synthesis, but not on protein synthesis.
2. The inhibitory effect on free radical chain reactions, because most carotenoids are lipid-soluble and might act as membrane-associated high-efficiency free radical scavengers.
3. The metabolic conversion of naturally occurring carotenoids to retinoids.

4. The interaction of carotenoids with topoisomerase II, an enzyme involved in cellular DNA-protein interaction. Thus, although several hypotheses have been put forward, the exact mechanism(s) of anticarcinogenic and antitumor effects of saffron and its main constituents are not clear at present.

CONCLUSION

Saffron and its main carotenoid constituents may have the potential to prevent and to treat of certain forms of cancer. Comprehensive and in-depth studies necessary to be conducted further along the following lines:

To determine the biological active ingredients of saffron, responsible for its anticancer effect.

To carry out epidemiological studies on effect of saffron against cancer.

To investigate the molecular mechanism(s) involved in the antitumor and anticancer effects of saffron.

To define efficacy and safety of saffron and its main ingredients for cancer prevention and treatment both in animal models and clinical trials.

Unfortunately, we spent many years and money focusing on cures of cancer, but focusing on prevention by natural anticancer agents instead would make the war on this terrible disease winnable. Chemoprevention of cancer is most challenging task in the 21st century and we need more knowledge regarding the relationship between natural products and this terrible disease.

From 1847 to 2005 we find 290 published scientific articles on different aspects of saffron, 20 books and many other information. From 1991 to 2005 were published 35 articles on antitumor effects of saffron and from 1993 to 2004 11 review articles on biological effects of saffron.

Results of these and new research on saffron will provide to construct a logical platform for the appearing of a new scientific discipline to be called: "SAFFRONOLOGY".

During Round Table: Industrial Perspectives for Saffron [I International Symposium on Saffron Biology and Biotechnology (Albacete, Spain, 2003)] I mentioned that from three main markets for saffron consumption: Industry (food industry mainly); Catering (restaurants and Public (end users): " the main increase will come from final users. If we can prove that saffron have medicinal properties, including anticancer activities, many people will pay more attention to this spice.

ACKNOWLEDGMENTS

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Table 1. Word Production of Saffron in 2004

Countries	Quantities (tons)	%
Iran	170	89,2
India	10	5,2
Greece	6	3,1
Morocco	1	0,5
Spain	0,5	0,26
Italy	0,1	0,05
Turkey	0,01	0,005
Other countries	3	1,6
Total	190,6	100

Table 2. Experimental publications on antitumor or anticancer effect of saffron in 2003-2004

Year	Authors	Journal	Country
2003	Premkumar K,	Phytother Res 17(6): 614-617	India
2003	Abdullaev FI,	Toxicol in Vitro 17(5-6):731-736	Mexico
2003	Abdullaev FI	Arch Med Res 34:354.	Mexico
2004	Das I, l	Asian Pac J Cancer Prev 5 (1).70-76	India
2004	Ochiai T	Neurosci Lett 362(1):61-64	Japan
2004	Ochiai T	Neurochem Int 244(5):321-30	Japan

Table 3. Review articles on the biological effects of saffron

Year	Authors	Journal/Book	Country
2000	Winterhalter P, Straubinger M	Food Rev Int 16(1): 39-59	Germany
2002	Deng Y, et al	Zhongguo Zhong Yao Za Zhi 27(8): 565-568	China
2002	Abdullaev FI	Exp Biol Med 227(1): 20-25	Mexico
2003	Abdullaev FI	Recent Progress in Medicinal Plants 8, 69-82	Mexico/Azerbaijan
2004	Abdullaev FI, Espinosa-Aguirre JJ	Cancer Detection & Prevention 28 (6): 426-432	Mexico
2004	Fernández JA	Recent Res Develop Plant Sci 2:127-159	Spain
2004	Giaccio M	Crit Rev Food Sci Nutr 44 (3):155-172	Italy