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Anticancer, Antimutagenic and Antioxidant Potential of Saffron: An Overview of Current Awareness and Future Perspectives

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ABSTRACT

Spices are dietary constituents consumed daily by most of the world population to enhance the flavor or taste of food. Saffron, obtained from dried stigmas of *Crocus sativus* L., is a commonly used spice for flavoring and coloring foods in different parts of the world. Since time immemorial, it has also been used in traditional medicine for various ailments. The chemical composition of saffron shows that it is a rich source of carotenoids. The three main chemical components of saffron are the bright yellow coloring carotenoids, crocin, a bitter taste, picrocrocin, and a spicy aroma, safranal. Crocetin and its semi-natural derivative, dimethylcrocetin (DMC), are also important carotenoids of saffron. During the past few years the anti-tumoural properties of saffron extracts, both *in vitro* and *in vivo*, have been demonstrated. *In vitro* investigations have reported saffron-mediated selective inhibition of the growth of tumor cells without damaging normal cells. A number of studies have demonstrated the saffron and its constituents exert a significant inhibition in the synthesis of DNA and proteins, and disruption of DNA–protein interaction on different malignant cells. Findings from various laboratories including ours have shown that saffron extract and some of its constituents possess antioxidant properties and can inhibit the genotoxicity or carcinogenicity of chemicals with various mechanisms of action. In view of the above findings and wide spread use of saffron, further research is needed to identify the active constituent(s) of saffron and elucidate the mechanism of action. This review provides an overall view on the biological properties of saffron with special emphasis on its anticancer, antimutagenic and antioxidant potential thus providing current awareness on saffron in biology and medicine and possible future perspective.

Keywords: anti-genotoxicity, carotenoids, chemoprevention, crocetin, crocin, *Crocus sativus*, saffranal

CONTENTS

INTRODUCTION

Saffron, the dried and dark red stigmas obtained from the flowers of *C. sativus* L., is an ancient, mystical spice that has been in use since the Greek-Minoan civilization. It has been historically used as a food colourant, drug in medicine and in cosmetics (Mathew 1982; Basker and Negbi 1983; Bowles 1985; Behnia *et al*. 1999). Numerous sources indicate that saffron cultivation is very old dating back to 2500–1500 BC, and originated possibly in Iran, Asia Minor or Greece and later became widespread in India, China, the Mediterranean basin and Eastern Europe (Tammaro 1987; Negbi 1999; Grilli *et al.* 2004). It is now largely cultivated in France, Greece, India, Iran, Italy, Spain, China, Israel, Morocco, Turkey, Egypt and Mexico for its flavoring and medicinal perspectives.

C. sativus is a perennial, stem less herb of the large *Iridaceae* family. It is a sterile triploid (Karasawa 1933; Ghaffari 1986; Rìos *et al.* 1996), probably derived from the wild species *Crocus cartwrightianus* (Mathew 1982; Grilli *et al.* 2004) and grows best often in friable, loose, well-watered and well-drained clay calcareous soils. The plant is characterized by its narrow leaves and a fleshy bulb called corm which is about 3 cm in diameter and approximately 8 g in weight. These corms play a vital role in the propagation of the plant as it fails to produce seeds upon selfing or crossing, due to its triploidy. Saffron flower, the source of spice, is purple colored with three thread-like reddish

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Mini-Review

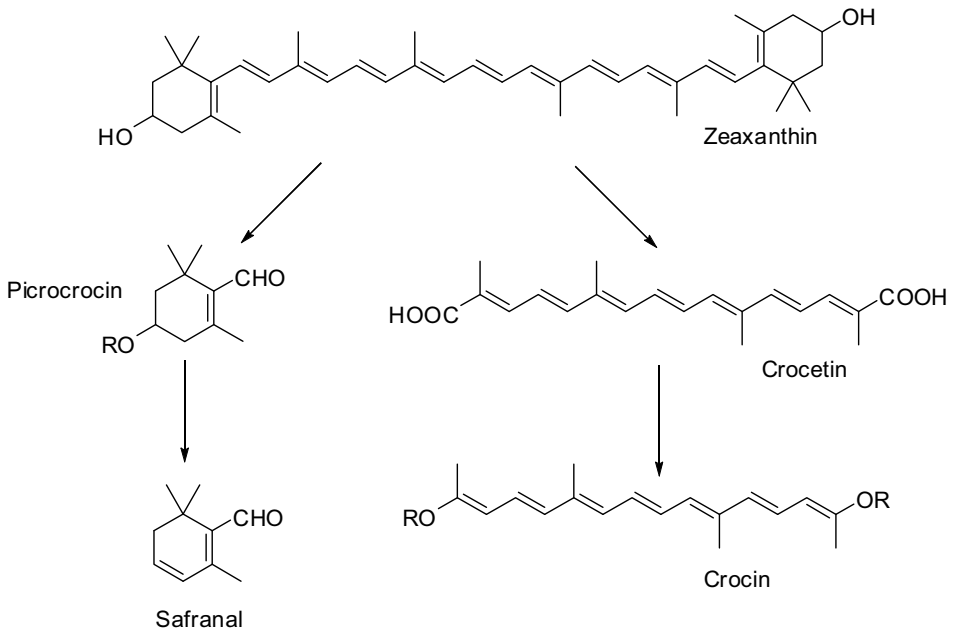

Fig. 1 Formation of saffron bioactive components from zeaxanthin bioactive cleavage.

coloured stigmas. These are collected, dried and processed to yield the most expensive spice (Rakesh *et al.* 2009).

Significant research has been conducted on the plant with the core interest of ascertaining its biologically active components and the possible mechanisms of their activity. These studies have concluded that saffron is the richest source of carotenoids and contains several volatile and non-volatile components derived from oxidative cleavage of carotenoids, of which the most important are: crocin, picrocrocin and safranal (Tarantilis *et al.* 1995; Escribano *et al.* 1996; Lozano *et al.* 2000). In addition, saffron contains proteins, sugars, vitamins, flavonoids and certain amino acids. It has now been recognized that the main constituents of saffron possess several pharmacological properties that can inhibit carcinogenesis (Nair *et al.* 1992; Escribano *et al.* 1996; Abdullaev and Espinosa-Aguirre 2004) and other major disorders in humans.

This review intends to provide an overall view on the biological activities of saffron to create awareness on its anticancer, antimutagenic and antioxidant potentials that can be explored and used as conventional and replacement therapies for treating various disorders in future.

ETHNO-MEDICAL IMPORTANCE

Saffron has not only been a primary spice but also a highly valued medicinal plant widely used in folk medicine. The therapeutic potential of saffron ranges widely, from treatment of simple ailments to treatment and prevention of obscure disorders. Traditionally it has been used as an antispasmodic, eupeptic, pain killer, anticatarrhal, carminative, diaphoretic, expectorant, stimulant, stomachic, aphrodisiac, and emmenagogue (Basker and Negbi 1983; Rios *et al.* 1996) and has shown profound effects against cramps, pain, asthma, bronchospasms, menstruation disorders, liver diseases, eye diseases and hypoxia. Evident reports show that saffron had been employed since ancient times to treat infertility and impotence (Abdullaev 2002; Chatterjee *et al.* 2005). Modern pharmacological studies reveals that saffron and its active components possess anti inflammatory, antitumor (Abdullaev 1993; Escribano *et al.* 1999a), antimutagenic, antioxidant, anti convulsant (Hosseinzadeh and Younesi 2002) and anti depressant potential (Hosseinzadeh *et al.* 2004). The crocin constituents has been reported to exert significant anti proliferation effects on certain human cancers (Aung *et al.* 2007). It has also been reported that crocin and safranal exhibit significant radical scavenging activity and thus act as potential antioxidants (Zhang *et al.* 1994; Abe *et al.* 1999). These reports suggest the potential of saffron as a remedy for major human diseases and provide a strong interest to explore the medicinal and nutritional significance of this valuable spice.

PHYTOCHEMISTRY

Over the past decade, significant progress has been made in evaluating the individual constituents of saffron and their pharmacological properties. Based on the studies from various laboratories, it has been concluded that saffron and extracts of saffron contains three main pharmacologically active metabolites that may be categorized as dyes (crocetin and crocins), bitter principle (picrocrocin) and volatile agents (safranal). Thus the color of saffron is attributed mainly to the degraded carotenoids (crocin and crocetin), and the flavor is derived from the carotenoid oxidation products (mainly safranal and the bitter glucoside picrocrocin). Pfander and Schurtenberger (1982) suggested that the biogenesis of these compounds occurs by bio-oxidative cleavage of zeaxanthin.

Crocins, the water-soluble carotenoids found in the stigma of the saffron are the most important and major compounds of saffron that have been shown to exert significant biological activities. The yellow pigment crocin containing a gentiobiose (disaccharide) group at each end of the molecule and its three other derivatives are the major colour compounds of saffron. The core compound of crocins is the crocetin which is a diterpenoid with a 20-carbon chain dicarboxylic acid. The five major biologically active ingredients namely, the four crocins and crocetin have been quantified by a simple, specific HPLC method (Li *et al.* 1999). Other minor carotenoids are also present in saffron besides the crocins.

Picrocrocin, a monoterpene glycoside is the chemical foremost contributing for the bitter taste of saffron. Picrocrocin [4-(β-D-glucopyranosyloxy)-2,6,6-trimethyl-1-cyclohexene-1-carboxaldehyde] (**Fig. 1**) is the degradation product of zeaxanthin and the precursor of safranal. During the drying process, for commercial purposes, picrocrocin liberates aglycone (HTCC, $C_{10}H_{16}O_2$) due to the action of the enzyme glucosidase. The aglycone is then transformed to safranal, a terpene aldehyde on dehydration. Safranal [2,6,6-trimethylcyclohexa-1,3-dien-1-carboxaldehyde], which is synthesized via deglucosylation of picrocrocin composes as much 70% of total volatiles and is responsible

for the odour and aroma distinctive of the plant. Thus, a good quality saffron may be said to consist of about 30% of crocins, 5 to 15% of picrocrocin and usually up to 2.5% of volatile compounds (Schmidt *et al.* 2007).

Additionally, 2-hydroxy-4,4,6-trimethyl-2,5-cyclohexadien-1-one, is one more element considered as powerful contributor to saffron's fragrance despite its being present in a lesser quantity than safranal (Jessie and Krishnakantha 2005). Furthermore, evidences support the presence of proteins, sugars, vitamins (especially riboflavin and thiamin), flavonoids, amino acids, minerals, gums, and pigments including, anthocyanin and lycopene in *C. sativus* (Abdullaev 1993; Ríos *et al.* 1996; Winterhalter and Straubinger 2000; Giaccio 2004).

CURRENT AWARENESS ON PHARMACOLOGY

Although saffron has wide-ranging therapeutic benefits, much research has been focused on its antioxidant, anti mutagenic and anti tumoral properties. A brief appraisal on the promising saffron research, directing its future role as a potential pharmacological source, has been reviewed in this paper.

Anti oxidative activities

Polyunsaturated fatty acids making up the lipid bilayers of cell membranes, expose them at a greater risk to peroxidetion. Free radical reactions in the lipid bilayer have been indicated to result in membrane damage and thereby alteration and impairment of membrane functions (Wiseman 1996) leading to adverse effects including atherosclerosis and cancer (Cook and Samman 1996; Schmidt *et al.* 2007). Reactive oxygen species stimulating oxidative damage to cellular macromolecules have been reported in association with various pathological conditions. Antioxidant therapy has been well documented to protect against such injuries (Love 1999; Gilgun-Sherki *et al.* 2002). Interestingly, saffron has been recommended for its free radical scavenging property that inhibits the lipid peroxidation (Tyler 1975; Halliwell and Gutteridge 1984; Rios *et al.* 1996).

It has been suggested that safranal has an overall protective effect against cerebral ischemia/reperfusion injury-induced oxidative stress in a rat model. It is evident from the conclusions of Magesh *et al.* (2006) that crocetin inhibits lipid peroxidation and increase antioxidant status by enhancing the glutathione activity. Hosseinzadeh and Sadeghnia (2005a) have measured the effect of safranal on lipid peroxidation in terms of malondialdehyde (MDA), a stable metabolite of the free radical-mediated lipid peroxidation cascade. Safranal reversed the increase in the MDA levels confirming its antioxidant role in Ischemia reperfusion injury (IRI). The same group have also evaluated the antioxidant potential of hippocampus homogenate samples following IRI, using ferric reducing antioxidant power (FRAP) assay. Experiments have also revealed that the component(s) of saffron extract inhibit lipid peroxidation in human platelet membranes induced by iron-ascorbic acid system (Jessie and Krishnakantha 2005). The effect of crocin and the aqueous saffron extract against renal IRI has been assessed by measuring the MDA levels and total thiol concentration (Hosseinzadeh *et al.* 2005b). The results have shown that the saffron extract was more potent than crocin which may be attributed to the presence of extensive constituents (crocins, crocetin, dimethyl crocetin and flavonoids) having the potential to quench free radicals.

Studies from our laboratory have shown that aqueous extract of saffron protects antitumor agents induced genetic damage (Premkumar *et al.* 2006) and also inhibits the genotoxin-induced oxidative stress in mice liver and increase the levels of glutathione (GSH) concentration, glutathione *S*-transferase (GST), glutathione peroxidase (GPx), catalase and superoxide dismutase (SOD) activities (Premkumar *et al.* 2001, 2003).

It has been well known that reactive oxygen species (ROS) also cause lipid peroxidation in the sperm cell membrane, impairing the sperm motility and its efficiency to fuse with the oocyte (Bolle *et al.* 2002; Agarwal *et al.* 2008). However antioxidants preserve fatty acids from oxidation, and therefore, have been implicated to play an important role in male fertility (Bolle *et al.* 2002). In view of these, Heidary *et al.* (2008) conducted a minor study to reveal the positive effect of saffron and its constituents, crocetin and dimethyl crocetin, on semen parameters such as motility and morphology (Heidary *et al.* 2008).

Anti-tumor and anti-mutagenic activities

A wide variety of naturally occurring substances including spices (Van Popper 1993) have been shown to inhibit chemical carcinogenesis in animal models (Williams 1984; Boone *et al.* 1990; Winterhalter and Straubinger 2000). One candidate spice, research on whose effect on neoplastic cells has seen a renaissance in the last decade is saffron. A growing body of evidence suggests the chemopreventive effects of saffron and its extracts, both *in vivo* and *in vitro* (Salomi *et al.* 1990, 1991a; Nair *et al.* 1991b, 1994, 1995; Abdullaev *et al.* 2000; Abdullaev 2002; Abdullaev *et al.* 2002; Das *et al.* 2004). Saffron has been quoted as a potential agent for reducing cisplatin-toxic side effects (Fernández *et al.* 2000) including nephrotoxicity. Oral administration of saffron extract have shown marked inhibition of growth of ascite tumors derived from sarcoma-180 (S-180), Ehrlich ascites carcinoma (EAC), Dalton's lymphoma ascites (DLA) in a dose-dependent manner and thereby increased the life span of the drug treated tumor-bearing mice (Nair *et al.* 1991a). Later reports have confirmed that oral administration of saffron extract suppressed the growth of DLA and S-180 tumour cells but did not affect the growth of EAC tumour cells in mice (Nair *et al.* 1992).

Numerous studies have demonstrated antitumor effect of saffron and its constituents on various malignant cells *in vitro*. The differences in sensitivity observed (**Table 1**) can be attributed to the distinct cellular properties or the methods of determination of cytotoxicity. It has been shown that nucleic acid synthesis was inhibited by saffron and its extracts without any profound effect on protein synthesis in tumor cells (Abdullaev and Frenkel 1992b; Nair *et al.* 1992). Evidence also supports the stimulatory effect of saffron extract on non-specific, *in vitro* proliferation of immature and mature lymphocytes and colony formation of normal human lung cells (Abdullaev and Frenkel 1992a; Nair *et al.* 1992).

Saffron extract has shown to be potential Cytotoxic on murine tumor cells (S-180, EAC, DLA), mouse leukemia cells (P388), Osteo and ovarian sarcoma, human cervical cancer (HeLa), adeno-carcinoma (A549), lung cancer (WI-38VA), human rhabdomyosarcoma (A-204), liver cancer (HepG-2), and colon cancer (SW-480) at IC_{50} value ranged as 7-200 µg/ml. Bioactive metabolites of saffron such as crocin, crocetin and picrocrocin also shown lower IC_{50} concentration on human leukemia cells. Other metabolites and extracts of saffron such as β-carotene, safranal, all-*trans* retinoic acid, saffron proteoglycan, saffron corm callus extract, glucoconjugate from saffron corms are cytotoxic to cervical cancer, fibro-sarcoma and breast cancer (Abdullaev *et al.* 2002).

Significantly, crocetin is the most studied saffron component that has been consistently linked to low the risk of cancer (Magesh *et al.* 2006). It has been reported that crocin decreased tumor growth (adenocarcinoma of the colon) and enhanced the survival in female rats without any significant effects in male animals, suggesting the influence of hormones on drug action (García-Olmo *et al.* 1999). As well the non mutagenic property of crocin and dimethyl-crocetin has been indicated using the Ames assay.

Antitumor activity of crocetin has been studied by Magesh *et al.* (2006). In their experiments, the effect of crocetin against tumor progression in lung-cancer bearing mice has been elaborately considered with reference to tumour incidence, antioxidant enzymes, marker enzymes and histo-

Table 1 Cytotoxic effect of saffron and its components on human malignant cells.

Agents	Cells	References
Saffron extract	HeLa; A549; WI-38VA	Abdullaev *et al.* 1992a, 1992b
Saffron extract	A-204; HEPG-2; SW-480	Abdullaev *et al.* 2003
Saffron extract, picrocrocin, safranal	HeLa	Escribino *et al.* 1996
Saffron corm callus extract and saffron proteoglycan	HeLa, fibrosarcoma, and breast carcinoma	Escribino *et al.* 1999a, 1999b, 1999c; Escribino *et al.* 2000; Fernández *et al.* 2000
Glucoconjugate from saffron corms	Tobacco BY-2 cells, protoplasts	Fernández *et al.* 2000
Crocin	HL-60; K562; HeLa; and HT-29, DHD/K12-PROb	Morjani *et al.* 1990; Tarantilis *et al.* 1994; Escribino *et al.* 1996; García-Olmo *et al.* 1999
Crocetin, dimethyl crocetin	HL-60; K562	Morjani *et al.* 1990; Tarantilis *et al.* 1994
β-Carotene	K562	Morjani *et al.* 1990
Saffron extract	Glucose-induced PC12 cells	Mousavi *et al.* 2010
Saffron extract	S-180; EAC; DLA; P388 osteosarcoma; ovarian sarcoma	Nair *et al.* 1991a; Salomi *et al.* 1991b; Nair *et al.* 1992, 1995
All-*trans* retinoic acid	HL-60	Tarantilis *et al.* 1994

pathological analysis. The decrease in the activities of the marker enzymes on treatment with crocetin has suggested its antineoplastic property that offers protection against abnormal cell growth (Verma and Bordia 1998). Another study has indicated the inhibitory action of crocetin at non toxic doses on the genotoxic effect and neoplastic transformation induced by benzo(a)pyrene in C3H1OT1/2 cells (Chang *et al.* 1996). Both these results have demonstrated that crocetin does not exhibit any genotoxicity. Two studies (Morjani *et al.* 1990; Tarantilis *et al.* 1995), have indicted the cytotoxic activity of crocetin on tumor cells. In contrast, another study has shown that crocetin did not exhibit any cytotoxic effect (Escribano *et al.* 1996). Previously, work carried out by Abdullaev's laboratory has also demonstrated that crocetin possessed no cytotoxic effect on colony formation of different tumor cells, but had an inhibitory effect on DNA, RNA, and protein synthesis (Abdullaev 1994). Reports have also confirmed that saffron extracts in combination with eminent antitumor agents such as selenium compounds caused a more effective inhibition of colony formation and nucleic acid synthesis (Abdullaev and González de Mejia 1995-1996). The strong anti tumor activity of crocetin is thus well established making it a candidate compound that can be tested for its effects against several other cancer systems.

Apart from the main components of saffron stigma, a novel glycoconjugate from corms and callus of saffron has been shown to possess cytotoxic activity against different tumor cells derived from fibrosarcoma, cervical epithelioid carcinoma, and breast carcinoma (Escribano *et al.* 1999b, 2000). The glycoconjugate has shown about eight times more cytotoxic for malignant cells causing plasma membrane damage in these cells. However, DNA fragmentation analysis has indicated the absence of apoptosis mediated cell death (Escribano *et al.* 1999c, 2000; Fernández *et al.* 2000).

The antimutagenic, comutagenic and cytotoxic effects of saffron and its ingredients has been assessed using the Salmonella test system, *in vitro* colony formation assay and four different cultured human normal (CCD-18Lu) and malignant (HeLa, A-204 and HepG2) cells (Abdullaev *et al.* 2003). In the *Salmonella* test system, saffron has exhibited non-mutagenic and non-antimutagenic activity against BP-induced mutagenicity. A dose-dependent co-mutagenic effect on 2-AA-induced mutagenicity has also been observed that is reported to be due to the saffron component, safranal. Saffron has displayed inhibition of colony formation only against human malignant cells and cytotoxicity against *in vitro* tumor cells.

Anti-cancer activity

Several reports on the anticarcinogenic effects of saffron have been put forward in the last decade (Salomi *et al.* 1991b; Dufresne *et al.* 1997). Ethanolic extract of saffron have shown to exert significant inhibitory action on colony formation and DNA and RNA synthesis in Hela cells (cervix epitheloid carcinoma cells (Abdullaev and Frenkel 1992b). Another study performed by the same group on A549 cells (lung adenocarcinoma cells), WI-38 (normal lung fibroblast-like cells), and VA-13 (WI-38 cells which were transformed by SV-40 viruses) has presented higher sensivity to the inhibitory action of saffron in comparison with normal counterparts (Abdullaev and Frenkel 1992a). *In vitro* inhibitory action of saffron stigma aqueous extract on the proliferation of human TCC and mouse L929 cells in a dose dependent manner has been studied (Isa 1992).

A study conducted for testing the efficacy of *C. sativus* extract and its major component crocin against three colorectal cancer cell lines (HCT-116, SW-480, and HT-29) has demonstrated significant inhibition on the cancerous cell growth (Aung *et al.* 2007). Various conclusions derived from this study include that at cancer cell inhibitory concentrations, the extract did not affect non-cancer cells. Further comparison has shown that HCT-116 cell line had a higher sensitivity to saffron extract and crocin than other two cells, SW-480 and HT-29. As the HCT-116 cells are p53 wild-type cells, the strong reaction of crocin and saffron extract on them suggests that p53 activity may be associated to the compounds present, exerting anticancer effects.

A great deal of interest has been shown for the elucidation of possible mechanisms for the tumoricidal and anti cancer activities of saffron compounds. One proposed mechanism for the antitumor or anticarcinogenic action of saffron is its inhibitory effect on cellular DNA and RNA synthesis, but not on protein synthesis (Abdullaev and Frenkel 1992b; Abdullaev 1994; Nair *et al.* 1994, 1995; Abdullaev and González de Mejia 1995-1996). Inhibition of free radical chain reactions, indicating their antioxidant properties may be another possible mechanism for antitumor and anticancer activities (Tyler 1975; Palozza and Krinsky 1992; Nair *et al.* 1994, 1995; Dufresne *et al.* 1997; Abdullaev and Frenkel 1999; Li *et al.* 1999; Molnar *et al.* 2000; Violette *et al.* 2002). Metabolic conversion of naturally occurring carotenoids to retinoids is a third proposed mechanism by which the saffron exerts its antitumor effect (Tarantilis *et al.* 1995; Dufresne *et al.* 1997), but it has been recently reported this conversion is not a necessary condition for the anticancer activity (Smith 1998). And finally the cytotoxic effect of saffron is said be related to the interaction between carotenoids and topoisomerase II (Isa 1992; Nair *et al.* 1995; Smith 1998). The lectin content (Oda and Tatsumi 1993; Escribano *et al.* 2000b) can also be suggested for antitumor activity of saffron in addition to the reports suggesting the inhibitory effect of saffron on various cellular enzymes and their functions (Nair *et al.* 1992; Abdullaev and González de Mejia 1997; El Daly 1998; Kubo and Kinst-Hori 1999). Saffron cytotoxicity can also be attributed to apoptosis (Morjani *et al.* 1990) and a sharp increase in the level of intracellular SH compounds. Research on PC-12 cells, crocin inhibited cell growth by its effects on tumor necrosis factor alpha (Ochiai *et al.* 2004).

The exact mechanisms of the tumoricidal and anti-cancer effects of saffron, however, need to be established on a strong molecular platform to facilitate its clinical usage.

OTHER BIOLOGICAL ACTIVITIES OF SAFFRON

Anti-depressive effects

Aqueous and ethanolic extracts of saffron and its constituents safranal and crocin have shown antidepressant effects in mice on intraperitoneal administration, using the forced swimming test. Safranal and crocin are reported to contribute to the antidepressant effect. The possible mechanisms proposed for safranal and crocin seems to be via inhibition of serotonin reuptake and inhibition of dopamine and norepinephrine re-uptake, respectively (Karimi *et al.* 2001; Hosseinzadeh *et al.* 2004). Additionally, crocin has been found to antagonize ethanol-induced depression via NMDA-receptor, *in vitro* (Abe *et al.* 1998).

Antinociceptive and anti-inflammatory activities

An *in vitro* study (Hosseinzadeh and Younesi 2002) indicates that the antinociceptive and anti-inflammatory activity of aqueous and ethanolic extracts of petals and stigma of *C. sativus*. Antinociceptive studies including the hot-plate test (55 ± 0.2°C) and writhing tests assessed on saffron pretreated mice have revealed interesting results suggesting the anti nociceptive effect of the stigma and petal extracts.

Anti-inflammatory studies carried out with xylene-induced inflammation (ear edema) in mice have shown the absence of increase in weight signifying the anti-inflammatory activity of the stigma and petal extracts (Hosseinzadeh and Younesi 2002). Another study with formalin induced inflammation conducted with six groups of rats treated with the extracts has also shown negative results for inflammation thus proving the anti-inflammatory effects of *C. sativus* stigma and petal extracts. The significant antinociceptive and anti-inflammatory effects of the petal extracts can be attributed to the flavonoid content, tannins and anthocyanins. Recent studies have recognized crocins and *Crocus* glycosides, to exhibit anti-inflammatory effect in some models of inflammation.

Effect on learning abilities and memory

The oral administration of saffron extract has showed distinct improvement of the ethanol pre-damaged memory of mice, although no effect on learning abilities in the passive avoidance test has observed. This effect is attributed to crocin, which has been proved to improve cognitive functions in animals whose memory had been experimentally impaired (Sugiura *et al.* 1994, 1995).

FUTURE PERSPECTIVES

Chemoprevention involves pharmacological intervention with specialised agents, both synthetic and natural, to reverse, repress, or prevent human cancers. The key crisis in employing synthetic chemopreventives in cancer treatment is the potential toxicity of these drugs to surrounding healthy cells. A possible approach to solve this problem is to pursue the 'back-to-nature' trend and explore the potential of plant and plant based dietary products against tumorigenesis. Evidences have shown that saffron and its components can affect carcinogenesis and is currently being studied at length as the most promising cancer chemopreventive agents. With the increasing need/requirement for natural chemopreventive agents for treating cancer and also various other diseases worldwide, a new strategy must be devised for the assessment of drug efficacy, effectiveness and toxicity of the medicinal compounds in saffron for optimization of its therapeutic potential.

Comprehensive studies determining biologically active components of saffron and defining the mechanism(s) involved in cancer chemoprevention need to be conducted in order to promote the use of saffron in cancer therapy. The inhibitory effect of saffron extract in combination with other synthetic drugs can also be exploited to provide evidence for a combinational therapy against tumours. Also, since current research has proved the anti-tumoural properties of saffron extracts, both *in vitro* and *in vivo*, it is necessary that future research needs to focus on performing human studies and clinical trials to define efficacy of saffron in cancer treatment and prevention.

In addition to the discovery of core components and their mechanisms of action, studies to investigate suitable drug delivery systems and to increase the effectiveness of the drug may also be conducted. The application of nanoparticles (NPs) to facilitate targeted delivery of the saffron components drug and their slow release is yet another interesting area for future research. However, the scarcity, sterility and expense in obtaining saffron may impede its usage in chemo prevention. Hence, considerable agronomic research to develop new production technologies of the plant may also be anticipated. Identification of novel methods to increase the production of therapeutic components in saffron by biotechnological methods such as enzyme conversion, callus induction and elicitation with natural elements can also be a part of such research.

Thus these various aspects afford a sincere hope that saffron will contribute to public health in the new century and also lay the platform for the emergence of a new scientific discipline that can be referred as *saffronology*.

SUMMARY

Saffron, the vernacular name for *C. sativus*, is the most precious and most expensive spice in the world. From time immemorial the spice has been cited in many indigenous and home-grown systems of health care for treatment of a wide-range of diseases and disorders. Modern pharmacological research have been intended to investigate the chemical constituents and their biological activity to confirm these traditional claims and they have confirmed the antioxidant, anti tumor and anti-depressant properties of the plant. Still there are many compounds in saffron with therapeutic potential in their unexplored fold. If future research is focused on exploring these potential compounds and developing the same into rational phytomedicines, saffron and its constituents will certainly serve as alternative anticancer agents, which alone and in combination with other synthetic drugs, may aid in the prevention and the treatment of existing and new forms of cancer. If future research is focused on unraveling these potential compounds and developing the same into rational phytomedicines, saffron is sure to become an important and integral part of therapeutic medicinal field leading to the development of safe and efficacious anti-cancer therapy. If future research is focused on unraveling these potential compounds and developing the same into rational phytomedicines, saffron will certainly become an important source and integral part of chemopreventive and alternative medicine.

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