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Review

Saffron: A repository of medicinal properties

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Saffron (stigmas of *Crocus sativus* L.) has been used for medicinal purposes since decades. Modern pharmacological research confirms large parts of traditional knowledge regarding the medicinal effects of saffron. With the recent availability of aqueous extracts with reproducible composition and preparation according to pharmacopoeial standards, the foundations for a development of saffron extracts into rational phytomedicines have been laid.

Key words: Saffron, medicine, stigma, properties.

INTRODUCTION

The word saffron originated from the 12th century old French term Safran, which was derives from the Latin word safranum. It is also related to the Italian Zafferano and Spanish Azafran (Harper, 2001). Safranum comes from the Arabic word asfar which means “yellow” (Katzer, 2001; Kumar 2006). Saffron (*Crocus sativus* L.) is a bulbous perennial spice belonging to family Iridaceae and popularly known as golden condiment. The plant does not propagate by seeds; the underground portion, corms (also called bulbs), divide to produce new plants. Flowers emerge in autumn; the outstanding feature of the lilac to mauve colored flower is its three stigmas 25 - 30 mm long, which droop over the petals, that is what is collected as saffron. There are also three yellow stamens, which lack the active compounds and are not collected. The stigma is attached to a style, which has little of the active components and is only included with the lower grades of saffron. Each bulb produces from one to seven flowers. The cultivated form is thought to have originated as a naturally occurring hybrid that was selected for its extra-long stigmas and has been maintained ever since. It takes about 36,000 flowers to yield just 1 pound of the stigmas.

Saffron believed to have originated from Greece, Asia Minor and Persia spreading eastwards to Kashmir and China. Its cultivation in the world extends through 0 to 90 °E longitude (Spain to Kashmir) and 30 - 45 °N latitude (Persia to England). Today saffron is cultivated from Eastern Mediterranean (Spain) to India (Kashmir) and is unknown in wild state (Mathew, 1999). As far as Kashmir is concerned, the saffron cultivation started in the reign of king Laltaditya during 550 A.D. In “Tozaki-jahangari” some reference has been made regarding saffron famous Kashmiri vaids namely Vegbhatta and sushtra used saffron as an ingredient of fragnance, as dye and in herbal medicine. Ancient texts on ayurveda have information about the herb’s use as an aphrodisiac. It is a stimulant and promotes libido that probably explains the kesar milk (Saffron mixed with milk) that is a part of the wedding night ritual.

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. 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 as a strengthening agent for the heart and as a cooling agent for the brain. It has been found beneficial in the treatment of urinary problems. It acts as a diuretic if soaked over-night in water and administered with honey. The spice is useful in promoting and regulating menstrual periods. It soothes lumbar pains, which accompany menstruation. Saffron is also beneficial in the treatment of other ailments concerning women such as leucorrhoea and

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Table 1. Saffron (*C. sativus*) nutritional value per 100 g.

Principal	Nutrient Value	Percentage of RDA%
Energy	310 Kcal	15.5
Carbohydrates	65.37 g	50
Protein	11.43 g	21
Total Fat	5.85 g	29
Cholesterol	0 g	0
Dietry Fiber	3.9 g	10
Vitamins		
Folates	93 mcg	23
Niacin	1.46 mg	9
Pyridoxine	1.010 mg	77
Riboflavin	0.267 mg	20
Thiamin	0.115 mg	10
Vitamin C	80.8 mg	90
Vitamin A	530 IU	18
Electolytes		
Potassium	1724 mg	37
Sodium	148 mg	10
Minerals		
Calcium	111 mg	11
Copper	0.328 mg	37
Iron	11.10 mg	139
Magnesium	264 mg	66
Manganese	28.408 mg	1235
Phosphorus	252 mg	36
Zinc	1.09 mg	10

Source: USDA national nutrient database.

hysteria. Pessaries of saffron are used in painful conditions of the uterus. Saffron oil is used as an external application in uterine sores.

In modern pharmacopoeias, saffron is employed only to color other medicines or as a cordial adjunct. It is a rich source of carotenoides due to which it has anti cancer and anti tumor properties. Research has revealed it to be rich in Vitamin-B2 and Riboflavin. The use of this spice rich in carotenoid for medical benefit has played an important role in traditional and folklore medicine of many cultures on the earth as a drug to treat various human health conditions (Abdullaev, 2002, 2003, 2004; Fernandez, 2004) (Table 1).

SOME MEDICINAL PROPERTIES OF SAFFRON

Antidepression effect

A number of recent preclinical and clinical studies indicate that stigma and petal of *C. sativus* have antidepressant effect. The antidepressant effect of *C. sativus* petal as well as stigma aqueous and ethanolic extracts has been shown in mice by Karimi et al. (2001). It was reported that two constituents of saffron, safranal and crocin, also have antidepressant activity in mice Hosseinzadeh et al. (2004). Recently, in small preliminary double-blind and randomized comparison of saffron and imipramine in the treatment of mild to moderate depression was demonstrated Akhondzadeh et al. (2005). In two other studies, the efficacy of petal of *C. sativus* in the treatment of mild-to moderate depression was confirmed Akhondzadeh Basti (2007) Moshiri (2006). Hosseinzadeh et al. (2007) results indicate that the saffron petal component, kaempferol, may be of valuable agent in the treatment of depression.

Effect on learning behavior and long-term potentiation

Memory is the ability of an individual to record the information and recall it whenever needed. Dementia is a mental disorder characterized by loss of intellectual ability (judgment or abstract thinking) which invariably involves impairment of memory. The most common cause of dementia is Alzheimers disease (AD), which is a progressive neurodegenerative disorder associated with loss of neurons in distinct brain areas and cord. Stressful conditions are often associated with loss of memory and cognitive functions which may lead to threats of schizophrenia and AD. Traditionally herbal drugs have been used to enhance cognitive functions and to alleviate other functions associate with the AD. A number of medicinal plants per se and medicines derived from these plants have shown memory enhancing properties by virtue of their medicinal constituents. *C. sativus* is one of the potent drug yielding herb as for as its medicinal properties are concerned. 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 (Jagdeep et al., 2009; 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 100 ml 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 et al., 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).

Anticonvulsant effect

Saffron has been reported to have some behavioral effects on the central nervous system. Zhang et al. (1994) reported that an alcoholic extract of *C. sativus* decreased the motor activity and prolonged the sleeping time induced by hexobarbital. This study suggests that the ethanolic extract possesses a sedative effect, which is probably responsible for the anticonvulsant effect of the extracts. 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).

Antigastric effects

C. sativus (saffron) suspension possesses antiulcerogenic principles which protect against gastric mucosal damage induced by indomethacin and necrotizing agent, through inhibition of gastric acid (attenuation of aggressive factors) and stimulation of mucus secretion (potentiation of defensive factors) in Shay rats. Probably the antiulcer effect is due, partly at least, to the presence of flavonoids in the saffron, although, the involvement of other compounds in saffron cannot be ruled out (Al-Mofleh et al., 2006). Hence, the prolong use of saffron in a small quantity in Arabian Coffee (Gahwa) as a flavoring agent and its use in oriental traditional medicine is substantiated by the results obtained in the present study as saffron also did not cause any apparent deleterious effects on the animals

Antiparkinsonian effect

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

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), Abdullaev (2002, 2003) demonstrated that the saffron extract itself in concentration up to 1500 mg/plate was non-toxic, non-mutagenic and non antimutagenic. 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

It has been reported that saffron or the compounds it contains, such as crocin and dimethylcrocin, are not mutagenic or genotoxic (Salomi et al., 1991a; Abdullaev et al., 2002, 2003). Premkumar et al. also showed that saffron aqueous extract protects from genotoxicity as well as genotoxins-induced oxidative stress in mice (Premkumar et al., 2001, 2003, 2006). In these studies, oral pretreatment with aqueous saffron extract (20, 40 and 80 mg/Kg) for 5 consecutive days significantly inhibited the genotoxicity of antitumor drugs (cyclophosphamide, mitomycin C and cisplatin), *in vivo*, as revealed by micronucleus and comet assay. It was suggested that saffron could exert its antigenotoxic and chemopreventive effects by the modulation of antioxidants and/or detoxification systems (Premkumar et al., 2001, 2006). It was also reported that crocetin could significantly inhibit the genotoxic effects and neoplastic transformations of C3H1OT1/2 cells by benzo (a)- pyrene (Chang et al., 1996). An inhibitory effect of safranal on MMS-induced genotoxicity has also been shown in multiple mice organs (Hosseinzadeh and Sadeghnia, 2007). The protective effects of saffron and crocin observed may be related to its antioxidant and radical scavenger properties. Saffron and crocin may also decrease the MMS-induced genotoxicity by enhancing the systems involve in detoxification and mutagen/ carcinogen inactivation (Hosseinzadeh et al., 2008). It has been shown that antioxidants reduced chemically

induced carcinogenesis (Khan et al., 2008) and inhibited DNA lesions induced by alkylating agents such as MMS (Kaya, 2003; Arranz et al., 2007). Saffron and its carotenoids scavenge free radicals and thereby may protect cells from oxidative stress (Bors et al., 1982; Abdullaev, 1993; Nair et al., 1995; Rios et al., 1996; Pham et al., 2000; Assimopoulou et al., 2005).

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 et al., 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 be 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 (ID50 of 3 mM) (Escribano et al., 1996).

Antihyperglycemic and pancrease- protective effects

Ethanolic extract of *C. sativus* L. stigmas when administered orally and intraperitoneally at different doses (20, 40, 80 mg $Kg^{-1)}$ caused a significant decrease of plasma glucose levels in diabetic rats and this effect was more potent after repeated intraperitoneal administration as, a marked normalization of blood glucose levels in these animals was achieved after 2 weeks of treatment (Daryoush et al., 2009). Assimopoulou et al. (2005) confirms that administration of *C. sativus* stigma extract function on the protection of vital tissues including pancreas, thereby reducing the causation of diabetes in these animals.

CONCLUSION

Plant extracts are some of the most attractive sources of new drugs and have been shown to produce promising results for the treatment of almost all of the diseases. As a therapeutic plant, saffron (*C. sativus* L. is a promising herb of pharmaceutical industry due to its varied medicinal properties ranging from mild fever to cancer and DNA repair.

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