Therapeutic properties of saffron and its chemical constituents

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ABSTRACT

Saffron (Crocus sativus L.) is a light purple flower with reddish colored stigma. It is one of the most expensive spices with a range of quality in its color and aroma. A few key countries involved in saffron commercialization are Spain, Iran, Greece, Morocco, India and China. The main chemical constituents found in saffron are safranal, picrocrocin, crocetin and its glycoside, crocins. These constituents have been reported with pharmacological activities largely responsible for abundant of health benefits. In this review, current findings on pharmacological activities of saffron and its main constituents were reviewed to support for the therapeutic role of saffron. Although adultery issues are commonly compounded problem in obtaining pure saffron, its health benefits as a chemopreventive and chemotherapeutic agent, effectiveness in the control of depression and anxiety, improvement in memory and endocrinological related issues have been supported by several clinical trials. Based on these research studies, saffron could be one of the significant natural products which needed much attention for its potential therapeutic roles.

Keywords: Saffron; Safranal; Crocins; Therapeutic benefits.

INTRODUCTION

Saffron (Crocus sativus L.) (Family-Iridaceae) is a well known popular spice for its color, aroma and flavor in cuisines of Middle East and Southern Europe countries. It is the dried red stigma of the purple flower of a perennial stem less plant. In Sanskrit, it is known as Kumkuma. Each flower has three red stigmas of saffron which are joined by the style.

Being a triploid and a male-sterile plant, it is propagated only by means of corms (Sampathu, et al., 1984). Strikingly, only four to five corms are produced per mother corm in one growing season, hence, the propagation rate is very slow. It is conservative in the region of Eastern Europe and Central Asia. The larger distance distribution of this species requires human help as its flowers cannot produce seeds to spread naturally. The botanical background and history of saffron reported that it spreads from the Mediterranean Sea over Persia to India (Schmidt, et al., 2007). Today, saffron products are marketed largely from Spain, Iran and a smaller scale from India, Greece and China.

Flowering of saffron happens in November and hence, collection of saffron stigmas begins with harvesting of flowers a few days after opening in the autumn. Then saffron...
stigmas are manually removed from flowers and this process does influence the quality and the price of saffron. Approximately, 150,000 to 220,000 flowers in quantity are required to produce 1 Kg of saffron (Schmidt, et al., 2007). Thus the overall process to obtain saffron raw materials contributes to the cost of saffron, the King of spices.

A wide variety of traditional therapeutic applications of saffron can be seen in Ayurvedic medicines, Persian traditional medicines (Karimi, et al., 2001), Tibetan and Traditional Chinese Medicines. Traditionally, saffron has been used for its antiseptic, antidepressant, digestive, anticancer and anticonvulsant activity. The previous literature review of saffron explored the agronomy, pharmacology, toxicity and interaction of saffron (Hosseinzadeh and Nassiri-As, 2013; Kumar et al., 2009; Srivastava, et al., 2010; Ulbricht, et al., 2011). Recently, significant number of pharmacological studies of saffron extract and its active constituents has been reported for its potential therapeutic roles in cancer, depression and memory loss. Therefore, this paper aimed to review the chemical constituents of saffron with their pharmacological properties reflected in current clinical trials, thus supporting its traditional therapeutic use.

CHEMICAL CONSTITUENTS OF SAFFRON

The chemical constituents of saffron have been studied and reviewed for decades. Saffron comprises more than 150 volatile and aroma-yielding compounds, inclusive of 40-50 volatiles components with strong odor (Srivastava, et al., 2010). It also contains many non-volatile constituents such as carotenoids, zeaxanthin, α and β-carotenes and lycopene (Liakopulou-Kyriakides and Kyriakides, 2002). The main important active constituents which have been used for quality of saffron and its pharmacological studies are cis and trans-crocin, crocetin, picrocrocin and safranal. These constituents are enzymatic oxidative metabolites of glucoside derivative of zeaxanthin, a carotenoid alcohol (all-trans-β-carotene-3,3′-diol) (Figure-1) which is commonly found in nature (Lourdes, et al., 2010).

Crocetin is a conjugated polyene with two carboxylic acid residues (Figure-1) which is insoluble in water but soluble in most organic solvents. It can also be presented as monoglycosyl and diglycosyl ester of crocetin which are hydrophilic and water soluble (Van Calsterren, et al., 1997). The crocetin esters such as all-trans-crocetin di-(β-D-gentiobiosyl) or α-crocin, all-trans-crocetin β-D-gentiobiosyl-β-D-glucosyl ester, all-trans-crocetin di-(β-D-glucosyl)ester, all-trans-crocetin mono-(β-D-gentiobiosyl)ester, 13-cis-crocetin β-D-gentiobiosyl-β-D-glucosyl ester are commonly found in saffron extract and they are known as crocins. Among the glycosyl ester of crocetin, the α-crocin, digentiobiosyl ester of the crocetin (Figure-1), is responsible for 10% of saffron’s mass and its distinctly bright yellow-orange color of saffron (Liakopulou-Kyriakides and Kyriakides, 2002).

On the other hand, crocins are unusual water-soluble carotenoids which are glucosyl esters of crocin (8,8′-diapocarotene-8,8′-dioic acid) glycosides. Being a member of carotenoids family, it is no doubt, the UV-Vis spectra of both all-trans and cis isomers of crocins show the characteristic of carotenoids with double peaks between 400 and 500 nm in the visible region (Figure-2). This characteristic has been used to verify all-trans glycosidic carotenoids of saffron with an additional band at 256 nm. As for the cis isomers, the first absorption band at 260 nm, the second band between 320 and 340 nm with medium intensity of absorption at 325 nm for 13-cis-carotenoids double bonds in the polyene conjugated system of crocin and lastly the third band between 400 and 500 nm with the maximum absorption at 435 nm are used as spectroscopic identification.

The constituents with organoleptic properties of the stigmen include picrocrocin (4-(β-D-glucopyranosyloxy)-2,6,6-trimethyl-1-cyclohexen-1-carboxaldehyde) and safranal (2,6,6-trimethyl-3-cyclohexadiene-1-carboxaldehyde) (Figure-1). Picrocrocin is a mono terpene glycoside precursor of safranal and it is responsible for the bitterness of saffron. The UV absorption pattern of picrocrocin includes a broad band at 250 nm with the maximum absorption at 254 nm (Alonso, et al., 2001). This pattern of UV absorption reflects for the presence of a α,β-unsaturated cycloaldehyde functional group in the molecular structure of
picrocrocin. Upon enzymatic or chemical hydrolysis, picrocrocin yields glucose and aglycone which is further dehydrated during the drying process to give safranal, the terpene aldehyde. Safranal is the main volatile substance responsible for the aroma of saffron (Tarantilis and Polissiou, 1997). Safranal with the UV absorption maximum of 330 nm (Alonso, et al., 2001) comprises up to 70% of dry saffron’s volatile fraction (Srivastava, et al., 2010). In fresh saffron, this substance exists as a stable picrocrocin but as a result of heat, it decomposes to the volatile aldehyde, safranal. Therefore, the content of safranal in samples would have correlated positively with the increasing temperature up to (80-90°C) during the dehydration process of plant materials (Carmona, et al., 2007).

Biological activities of these three main constituents of saffron extract have been investigated since last decade. It has been noted that current findings of its biological activities supported its medicinal use in traditional practices.

**POTENTIAL THERAPEUTIC PROPERTIES**

Potential therapeutic properties of saffron and its constituents include anti-genotoxic effect and cytotoxic effect against cancer cells, improving learning and memory skills, depression and anxiety control, erectile dysfunction and sexual behavior, cardiovascular diseases, hypoglycemic and anti-ulcer activities (Table 1).

**Anticancer activity:** Saffron is a rich source of carotenoids and is known to have anticancer and antitumor properties. A number of both *in-vivo* and *in-vitro* research findings had shown positive relationships between carotenoids and its inhibitory effect on the growth of DNA synthesis, and therefore it had obtained much attention from many researchers to study antitumor activity of carotenoid-based constituents found in saffron.

The *in-vivo* inhibitory effect of saffron on chemical carcinogenesis had been reported in early 1990s (Nair, et al., 1991; Salomi, et al., 1991). Subsequently, Abdullaev and Frenkel (1992), had studied the effect of saffron on intracellular DNA, RNA and protein synthesis in malignant and non-malignant human cells. A dose-dependent inhibition of crocin, safranal and picrocrocin against tumor cell growth using *in-vitro* assay on human cervical epithelioid carcinoma cells (HeLa) demonstrated its inhibition activity on the growth of human cancer cells (Escribano, et al., 1996). This study noted induced apoptosis activity of crocin as evidenced by morphological changes in cells; suggesting that crocin could be further studied for its anticancer property.

Although antitumor and chemopreventive potential of saffron was noted in early 1990s, there was no study developed on mechanism of action until Abdullaev and his team urged for the investigation on mechanism of its chemotherapeutic effect, its efficacy and safety in cancer treatment (Abdullaev, 2003). In 2002, Abdullaev and his team had proposed a few hypotheses on anticancer and tumoricidal mechanisms of saffron. The postulated mechanisms of action included inhibitory effects of saffron on DNA and RNA synthesis, inhibitory effect on the free radical chain *via* its antioxidant property, effect of its carotenoids on topoisomerase activity, and lastly, increasing the amount sulfhydryl containing compounds in cancer cells (Abdullaev, 2002).

Following these hypotheses on mechanisms of action of saffron for its chemotherapeutic activity, (Abdullaev, et al., 2003) demonstrated adose-dependent inhibitory effect of saffron against formation of tumor cells using Human Cervix Epitheloid Carcinoma cells (HeLa A-204) and CCD-18Lu (human normal lung cells). The outcome of this study supported for the involvement of carotenoid constituents in its anticancer activity.

On the other hand, genotoxicity of anticancer drugs had become concerned for developing secondary malignancies induced by side effects of anticancer drugs. Prem kumar et al., (2006) investigated the chemoprotective value of saffron in mice at doses of saffron (20, 40, 80mg/Kg) against cisplatin, cyclophosphamide and mitomycin C using the Comet assay. The study reported that pretreatment of saffron inhibited drug induced cellular DNA damage significantly. Drug induced DNA damage had been strongly associated with tumorigenesis and therefore it was concluded that saffron could be used as an adjuvant in chemotherapy.
Amin, et al., (2011) supported the chemopreventive property of saffron using both in-vivo and in-vitro studies in diethyl nitrosamine (DEN) induced liver cancer cells. The in-vivo experiment was based on saffron administration at doses of 75, 150, and 300mg/Kg/day. This study demonstrated anti-proliferative activity of saffron by presenting the inhibitory effect on both nodular and classical foci of altered hepatocyte (FAH) formation in the liver of DEN-treated rodents (Amin, et al., 2011). The observation was supported by in-vitro experimental findings on induced apoptosis, reduced cell proliferation rate, decreasing oxidative stress due to its strong anti-oxidant property of saffron and down-regulation of inflammatory markers. The above experimental findings indicated the involvement of modulating oxidative damage and anti-inflammation in heptocarinomas as a part of chemopreventive mechanism of action.

The antiproliferative properties of saffron extract and crocin was reported against human prostate cancer (D’Alessandro and Mancini, 2013) and human leukemia HL-60 cells (Sun, et al., 2013). Both studies concluded that crocin inhibited the respective cell proliferation, arrest cell cycle progression, inducing apoptosis in a time and concentration dependent manner.

**Improving learning and memory skills:** Akhondzadeh, et. al. (2010a; b) proposed saffron may inhibit the aggregation and deposition of amyloid beta in the human brain. This property of saffron was assessed in the treatment of mild to moderate Alzheimer’s diseases. Saffron extract and crocins had shown to prevent spatial learning and memory impairment caused by the effect of chronic-induced stress (Ghadrdoost, et al., 2011). The correlation between the antioxidant activity of saffron and impairment caused by oxidative stress, was one of the proposed mechanisms for saffron having preventive property against memory impairment.

A positive correlation between the enhancement of cognitive function and increase in total brain antioxidant activity supported by animal model (Papandreou, et al., 2011) clearly demonstrated the role of saffron. Furthermore, observation of attenuated scopolamine-induced spatial memory performance in mice upon the treatment with 15 and 30mg/kg of crocin, supported the effectiveness of saffron in cognitive function (Pitsikas, et al., 2007).

**Antidepressant activity:** At the same time, the antidepressant activity of saffron extract was shown to be equivalent to that of imipramine based on the double blind and randomized trial conducted by (Akhondzadeh, et al., 2004) over a period of six weeks. Furthermore, the efficacy of dried saffron extract (15mg) was noted to be comparable with the efficacy of fluoxetine (Akhondzadeh, et al., 2005; Noorbala, et al., 2005). In addition to the extract of saffron stigma, the extract of dried petal of saffron plant had shown to be effective in the treatment of mild to moderate depression based on the observation of six weeks randomized double blind clinical trial with 36 adult participants (Basti, et al., 2007; Moshiri, et al., 2006). These findings supported its traditional Persian medicine use in depression (Sarris, 2007).

**Anxiety and anticonvulsant activities:** Traditional use of saffron for anxiety and anticonvulsant activities was scientifically proven by using crocin in comparison with diazepam to control anxiety (Pitsikas, et al., 2008) and safranal as an anticonvulsant agent in animal studies (Hosseinzadeh, et al., 2005; 2007).

**Other therapeutic benefits of saffron:** As described in Persian traditional medicine, the use of saffron to treat menstrual disorder (Rios, et al., 1996) was supported by the psychological and physiological effect of saffron odor in women to treat premenstrual syndrome, dysmenorrhea and irregular menstruation (Fukui, et al., 2011). This study speculated that saffron odor may interfere with the level of sex steroid hormones to achieve anti-stress action. Saffron extract on the endocrine system was further supported by observation of reducing metabolic and behavior signs of stress in saffron treated rodents (Hooshmandi, et al., 2011).

Relating with the anti-stress function of saffron, it had been reported that saffron extract and crocin would improve erectile dysfunction (ED) and sexual behavior in male (Hosseinizadeh, et al., 2008). The outcome of this study benefited in improvement of ED function by saffron. The effect was noted to be equivalent to sildenafil which is clinically used for the treatment of ED due to its atrial vasodilation enhancement (Shamsa, et al., 2009). At the same time its hypotensive property had been further supported with the effect in lowering of blood pressure of rats by saffron and its constituents, safranal and crocin.
In another word, vasodilation property of saffron extract is not only responsible for its hypotensive effect but it would have attributed towards reducing anxiety, stress and improving erectile dysfunction.

The medicinal value of saffron had further extended from vasodilation property to delaying in progression of ischemic heart disease with the optimal dose of 400mg/Kg. Again this cardioprotective activity of saffron was expected to have attributed from its antioxidant properties (Yamauchi, et al., 2011). An association of saffron in heart diseases recently included the protective effect on lethal cardiac arrhythmias upon the pretreatment with saffron (100mg/kg/day) (Joukar, et al., 2013). In the management of metabolic syndrome diseases, the effect of crocin on the insulin resistance and lipid profile in induced diabetic rats had been reported recently (Shirali, et al., 2013). This supported the mechanism of the hypoglycemic actions of saffron thus enhancing glucose uptake and insulin sensitivity in muscle cells (Kang, et al., 2012). Lastly, it had been suggested that saffron, crocin and safranal would have indomethacin induced gastric ulcers preventive property (Kianbakht and Mozaffari, 2009).

CONCLUSION

Saffron and its active constituents have shown significant potential therapeutic benefits in the management of cancer, learning and memory loss, depression, anxiety control, erectile dysfunction (ED), sexual behavior, cardioprotective activities and hypoglycemic activities. As proposed by many studies, benefits possess by saffron is believed to be largely due to its anti-oxidant activities.

REFERENCES


### Table-1: A summary of potential therapeutic activity of saffron and its constituents.

<table>
<thead>
<tr>
<th>Therapeutic activity</th>
<th>Responsible active constituents</th>
<th>References</th>
</tr>
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<td>Premenstrual syndrome, Dysmenorrhea</td>
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<tr>
<td>Atrial vasodilation</td>
<td>Saffron extract</td>
<td>Shamsa, et al., (2009)</td>
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<td>Hypotension</td>
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<td>Gastric ulcers</td>
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Figure-1: Chemical structures of saffron constituents.

Figure-2: UV spectrophotometry spectra of sigma saffron extract (0.2mg/ml) with 70% v/v ethanol.