ISSN 0974 – 5211

Journal of Natural Products

Volume 7 (2014)

www.JournalofNaturalProducts.com

Review

Therapeutic properties of saffron and its chemical constituents

Gabriel Akyirem Akowuah[1], Thet Thet Htar[2*]

[1]School of Pharmacy, UCSI University, 56000 Kuala Lumpur, Malaysia

[2]Discipline of Pharmacy, Monash University Malaysia, Jalan Lagoon Selatan, 46150 Bandar Sunway, Kuala Lumpur, Malaysia

*Corresponding Author

(Received 12 May 2013; Revised 19 May-03 October 2013; Accepted 04 November 2013)

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* Linn.) (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 1Kg 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 as markers 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 crocetin (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-glucopyrannosyloxy)-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, genotoxcity 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 (Ríos, 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 effect 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 (Hosseinzadeh, 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

(Imenshahidi, et al., 2009). 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

Abdullaev, F.I., Frenkel, G.D., (1992): The effect of saffron on intracellular DNA, RNA and protein synthesis in malignant and non-malignant human cells. *Biofactors.*, 4:43-45.

Abdullaev, F.I., (2002): Cancer Chemopreventive and Tumoricidal Properties of Saffron (*Crocus sativus* L.). *Exp. Biol. Med*., 227:20-25.

Abdullaev F.I., (2003): *Crocus sativus* against cancer. *Arch. Med. Res.*, 34:354.

Abdullaev, F.I., Riveron-Negrete, L., Caballero-Ortega, H., Hernandez, J.M., Perez-Lopez, I., Pereda-Miranda, R., Espinosa-Aguirre, J.J., (2003): Use of in-vitro assays to assess the potential antigenotoxic and cytotoxic effects of saffron (*Crocus sativus* L.). *Toxicol. in Vitro.*, 17:731-736.

Akhondzadeh, S., Fallah-Pour, H., Afkham, K., Jamshidi, A.H., Khalighi-Cigaroudi, F., (2004): Comparison of *Crocus sativus* L. and imipramine in the treatment of mild to moderate depression: A pilot double-blind randomized trial. *BMC Complement Altern Med.*, 4:12.

Akhondzadeh, S., Tahmacebi-Pour, N., Noorbala, A.A., Amini, H., Fallah-Pour, H., Jamshidi, A-H., Khani, M., (2005): *Crocus sativus* L. in the treatment of mild to moderate depression: A double-blind randomized and placebo-controlled trial. *Phytother. Res.*, 19:148-151.

Akhondzadeh, S., Shafiee-Sabet, M., Harirchian, M.H., Togha, M., Cheraghmakani, H., Razeghi, S., Hejazi, S.S., Yousefi, M.H., Alimardani, R., Jamshidi, A., Zare, F., Moradi, A., (2010a): Saffron in the treatment of patients with mild to moderate Alzheimer's disease: a 16-week, randomized and placebo-controlled trial. *J. Clin. Ther.*, 35:581-588.

Akhondzadeh, S., Sabet, M.S., Harirchian, M.H., Togha, M., Cheraghmakani, H., Razeghi, S., Hejazi, S.S., Yousefi, M.H., Alimardani, R., Jamshidi, A., Rezazadeh, S.A., Yousefi, A., Zare, F., Moradi, A., Vossoughi, A., (2010b): A 22-week, multicenter, randomized, double-blind controlled trial of *Crocus sativus* in the treatment of mild-to-moderate Alzheimer's disease. *Psychopharmacology*, 207:637-643.

Alonso, G.L., Salinas, M.R., Sanchez-Fernandez, M.A., Garijo, J., (2001): Safranal content in Spanish Saffron. *Food. Sci. Technol. Int.*, **7**: 225-229.

Amin, A., Hamza, A.A., Bajbouj, K., Ashraf, S.S., Daoud, S., (2011): Saffron: A potential candidate for a novel anticancer drug against hepatocellular carcinoma. *Hepatology*, 54:857-867.

Basti, A.A., Moshiri, E., Noorbala, A.A., Jamshidi, A.H., Abbasi, S.H., Akhondzadeh, S., (2007): Comparison of petal of *Crocus sativus* L. and fluoxetine in the treatment of depressed outpatients: A pilot double-blind randomized trial. *Prog. Neuro-Psychoph.*, 31:439-442.

Carmona, M., Zalacin, A., Salinas, M.R., Alonso, G.L., (2007): A new approach to saffron aroma. *Crit. Rev. Food. Sci.*, 47:145-159.

D'Alessandro, A.M., Mancini, A., (2013): *Crocus sativus* stigma extract and its major constituent crocin possess significant antiproliferative properties against human prostate cancer. *Nutr. Cancer*, 65: 930-942.

Escribano, J., Alonso, G., Coca-Prados, M., Fernandez, J., (1996): Crocin, safranal and picrocrocin from saffron (*Crocus sativus* L.) inhibit the growth of human cancer cells *in vitro*. *Cancer Lett*., 100: 23-30.

Fukui, H., Toyoshima, K., Komaki, R., (2011): Psychological and neuroendocrinological effects of odor of saffron (*Crocus sativus*). *Phytomedicine*, 18:726-730.

Ghadrdoost, B., Vafaei, A.A., Rashidy-Pour, A., Hajisoltani, R., Bandegi, A.B., Motamedi, F., Haghighi, S., Sameni, H.R., Pahlvan, S., (2011): Protective effect of saffron extract & its active constituent crocin against oxidative stress and spatial learning and memory deficits induced by chronic stress in rats. *Eur. J. Pharmacol.*, 667:222-229.

Hooshmandi, Z., Rohani, A.H., Eidi, A., Fatahi, Z., Golmanesh, L., Sahraei, H., (2011): Reduction of metabolic and behavioral signs of acute strss in male Wistar rats by saffron water extract and its constituent safranal. *Pharm. Biol.*, 49:947-954.

Hosseinzadeh, H., Talebzadeh, F., (2005): Anticonvulsant evaluation of safranal and crocin from *Crocus sativus* in mice. *Fitoterapia*, 76:722-724.

Hosseinzadeh, H., Sadeghnia, H.R., (2007): Protective effect of safranal on pentylenetetrazol-induced seizures in the rat: Involvement of GABAergic and opioids systems. *Phytomedicine*,14: 256-262.

Hosseinzadeh, H., Ziaee, T., Sadeghi, A., (2008): The effect of saffron, *Crocus sativus* stigma, extract and its constituents, safranal and crocin on sexual behaviors in normal male rats. *Phytomedicine*, 15:491-495.

Hosseinzadeh, H., Nassiri-As, M.,(2013): Avicenna's (Ibn Sina) the Canon of Medicine and Saffron (Crocus sativus): A Review. *Phytother. Res.*, 27:475–483.

Imenshahidi, M., Hosseinzadeh, H., Javadpour, Y., (2009): Hypotensive effect of aqueous saffron extract (*Crocus sativus* L.) and its constituents, safranal and crocin, in normotensive and hypertensive rats. *Phytother. Res.*, 24:990-994.

Joukar, S., Ghasemipour-Afshar, E., Sheibani, M., Naghsh, N., Bashiri, A., (2013): Protective effects of saffron (*Crocus sativus*) against lethal ventricular arrhythmias induced by heart reperfusion in rat: A potential anti-arrhythmic agent. *Pharm Biol.*, 51:836-843.

Kang, C., Lee, H., Jung, E-S., Seyedian, R., Jo, M., Kim, J., Kim, J-S., Kim, E., (2012): Saffron (*Crocus sativus* L.) increases glucose uptake and insulin sensitivity in muscle cells via multipathway mechanisms. *Food Chem.*, 135:2350-2358.

Karimi, G., Hosseinzadeh, H., Khaleghpanah, P., (2001): Study of antidepressant effect of aqueous and ethanolic of *Crocus sativus* in mice. *Iran. J. Basic Med. Sci.*, 4:11-15.

Kianbakht, S., Mozaffari, K., (2009): Effects of saffron and its active constituents, crocin and safranal on prevention of Indomethacin induced gastric ulcers in diabetic and nondiabetic rats. *J. Med. Plants*, 6:30-38.

Kumar, R., Singh, V., Devi, K., Sharma, M., Singh, M.K., Ahuja, P.S., (2009): State of Art of Saffron (*C. sativus*) Agronomy: A Comprehensive Review. *Food. Rev. Int.*, 25:44-85.

Liakopulou-Kyriakides, M., Kyriakides, D.A., (2002): *Crocus sativus*-Biological active constituents. *Stud. Nat. Prod. Chem.*, 26:293-312.

Lourdes, G.G., Angela, R.M., Oussama, A., (2010): Understanding Carotenoid Metabolism in Saffron Stigmas:Unravelling Aroma & Colour Formation. *Func. Plant Sci. Biotech.,* 4:56-63.

Moshiri, E., Basti, A.A., Noorbala, A., Jamshidi, A., Abbasi, S.H., Akhondzadeh, S., (2006): *Crocus sativus* L. (petal) in the treatment of mild-to-moderate depression: A double-blind, randomized and placebo-controlled trial. *Phytomedicine*, 13:607-611.

Nair, S.C., Panikkar, B., Panikkar, K.R., (1991): Antitumor activity of saffron (*Crocus sativus*). *Cancer Lett.*, 57:109-114.

Noorbala, A.A., Akhondzadeh, S., Tahmacebi-Pour, N., Jamshidi, A.H., (2005): Hydro-alcoholic extract of *C. sativus* versus fluoxetine in the treatment of mild to moderate depression: a double-blind, randomized pilot trial. *J. Ethnopharmacol.*, 97:281-284.

Papandreou, M.A., Tsachaki, M., Efthimiopoulos, S., Cordopatis, P., Lamari, F.N., Margarity, M., (2011): Memory enhancing effects of saffron in aged mice are correlated with antioxidant protection. *Behav. Brain Res.*, 219:197-204.

Pitsikas, N., Zisopoulou, S., Tarantilis, P.A., Kanakis, C.D., Pollisou, M.G., Sakellaridis, N., (2007): Effects of the active constituents of *Crocus sativus* L. crocins on recognition and spatial rats' memory. *Behav. Brain Res.*, 283:141-146.

Pitsikas, N., Boultadakis, G.G., Tarantilis, P.A, Sakellaridis, N., (2008): Effects of the active constituents of *Crocus sativus* L., crocins in an animal model of anxiety. *Phytomedicine*, 15:1135-1139.

Premkumar, K., Thirunavukkarasu, C., Abraham, S.K., Santhiya, S.T., Ramesh, A., (2006): Protective effect of saffron (*Crocus sativus* L.) aqueous extract against genetic damage induced by anti-tumour agents in mice. *Hum. Exp. Toxicol.*, 25:79-84.

Rios, J.L., Recio, M.C., Giner, R.M., Manez, S., (1996): An update review of saffron and its active constituents. *Phytother. Res.*, 10:189-193.

Sampathu, S.R., Shivshankar, S., Lewis, Y.S., (1984): Saffron (*C. sativus*) cultivation, processing, chemistry & standardization. *CRC Crit. Rev. Food Sci. Nutr.*, 20:123-157.

Salomi, M.J., Nair, S.C., Pannikar, K.R., (1991): Inhibitory effects of Nigella sativa and saffron (*C. sativus*) on chemical carcinogenesis in mice. *Nutr. Cancer,* 16:67-72.

Sarris, J., (2007): Herbal medicines in the treatment of psychiatric disorders: a systematic review. *Phytother. Res.*, 21:703-716.

Schmidt, M., Betti, G., Hensel, A., (2007): Saffron in phytotherapy: pharmacology and clinical use. *Wien. Med. Wochenschr*., 157:315-319.

Shamsa, A., Hosseinzadeh, H., Molaei, M., Shakeri, M.T., Rajabi O., (2009): Evaluation of *Crocus sativus* L. (saffron) on male erectile dysfunction, a pilot study. *Phytomedicine.*, 16:690-693.

Shirali, S., Bathaie, S.Z., Nakhjavani, M., (2013): Effect of crocin on the insulin resistance & lipid profile of streptozotocin-induced diabetic rats. *Phytother. Res.*, 27:1042-1047.

Srivastava, R., Ahmed, H., Dixit, R.K., Dharamveer, S.A.S., (2010): *Crocus sativus* L.: A comprehensive review. *Pharmacogn. Rev*., 4:200-208.

Sun, Y., Xu, H-J., Zhao, Y-X., Wang, L-Z., Sun, L-R., Wang, Z., Sun, X-F., (2013): Crocin exhibits antitumor effects on human leukemia HL-60 cells in vitro and in vivo. *Evid. Based Complement. Alternat. Med.*, 2013:1-7.

Tarantilis, P.A., Polissiou, M., (1997): Isolation and identification of the aroma components from saffron (*Crocus sativus* L.). *J. Agric. Food. Chem.*, 45:459-462.

Ulbricht, C., Conquer, J., Costa, D., Hollands, W., Iannuzzi, C., Isaac, R., Jordan, J.K., Ledesma, N., Ostroff, C., Jill, M.,. Serrano, G., Michael, D., Shaffer, M.,(2011): An Evidence-Based Systematic Review of Saffron (*Crocus sativus*) by the Natural Standard Research Collaboration. *J. Diet. Suppl.*, 8:58–114.

Van Calsterren, M.R., Bissonnette, M.C., Comier, F., Dufresne, C., Ichi, T., Leblanc, J.C., Perreault, D., Roewer, I., (1997): Spectroscopic characterization of crocetin derivatives from *Crocus sativus* and *Gardenia jasminoides*. *J. Agric. Food. Chem.*,45: 1055-1061.

Yamauchi, M., Tsuruma, K., Imai, S., Nakanishi, T., Umigai, N., Shimazawa, M., Hara, H., (2011): Crocetin prevents retinal degeneration induced by oxidative and endoplasmic reticulum stresses via inhibition of capase activity. *Eur. J. Pharmacol.*, 650:110-119.

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

Therapeutic activity	Responsible active constituents	References
Chemotherapeutic activity	Saffron extract, Crocin, Safranal and Picrocrocin	Abdullaev and Frenkel (1992); Abdullaev,et al., (2003); D'Alessandro and Mancini(2013); Nair, et al., (1991); Salomi, et al., (1991); Sun, et al., (2013)
Chemopreventive and Genotoxicity	Saffron extract	Amin, et al., (2011); Premkumar et al., (2006)
Alzheimer's diseases, Memory enhancement	Saffron extract and Crocin	Akhondzadeh et al., (2010); Ghadrdoost, et al., (2011); Pitsikas, et al., (2007)
Anti-depressant activity	Saffron extract	Akhondzadeh, et al., (2004); Akhondzadeh, et al., (2005); Basti, et al., (2007); Moshiri, et al., (2006); Noorbala, et al., (2005)
Anxiety control	Crocin and Safranal	Pitsikas, et al., (2008); Hosseinzadeh, et al., (2005); Hosseinzadeh, et al., (2007)
Premenstrual syndrome, Dysmenorrhea	Saffron extract	Fukui, et al., (2011)
Metabolic stress	Saffron extract	Hooshmandi, et al., (2011)
Erectile dysfunction and Sexual behavior	Saffron extract and Crocin	Hosseinzadeh, et al., (2008)
Atrial vasodilation	Saffron extract	Shamsa, et al., (2009)
Hypotension	Saffron extract, Safranal and Crocin	Imenshahidi, et al., (2009)
Ischemic heart disease and Cardioprotective activity	Saffron extract	Joukar, et al., (2013); Yamauchi, et al., (2011)
Hypoglycemic activity	Saffron extract and Crocin	Kang, et al., (2012); Shirali, et al., (2013)
Gastric ulcers	Saffron extract, Crocin and Safranal	Kianbakht and Mozaffari (2009)

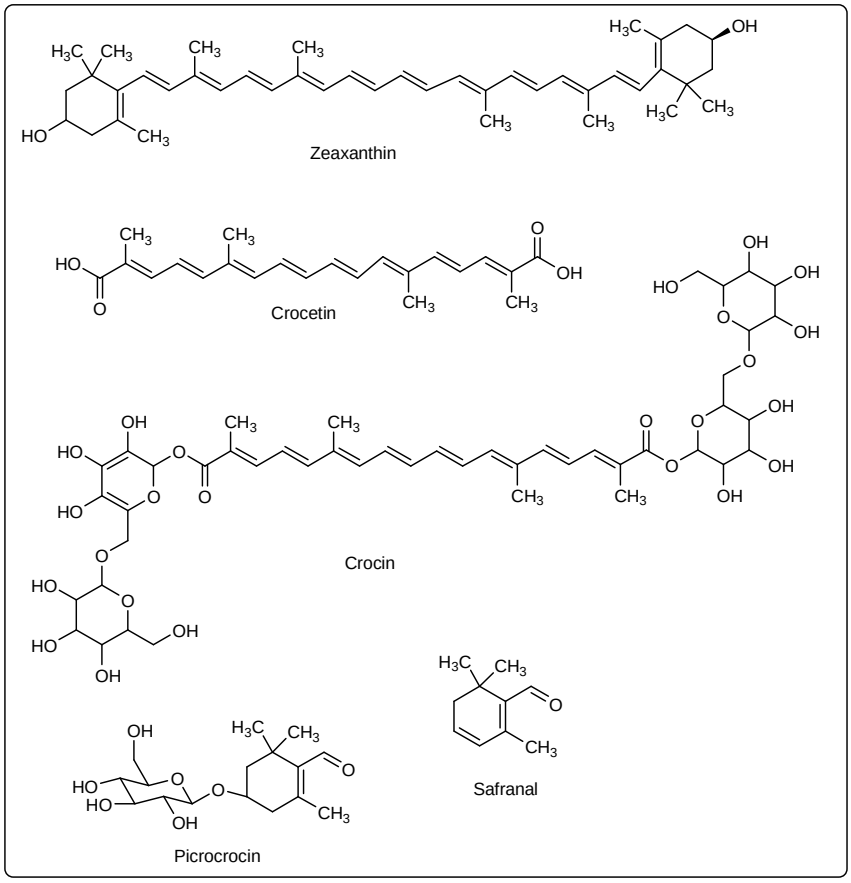

Figure-1: Chemical structures of saffron constituents.

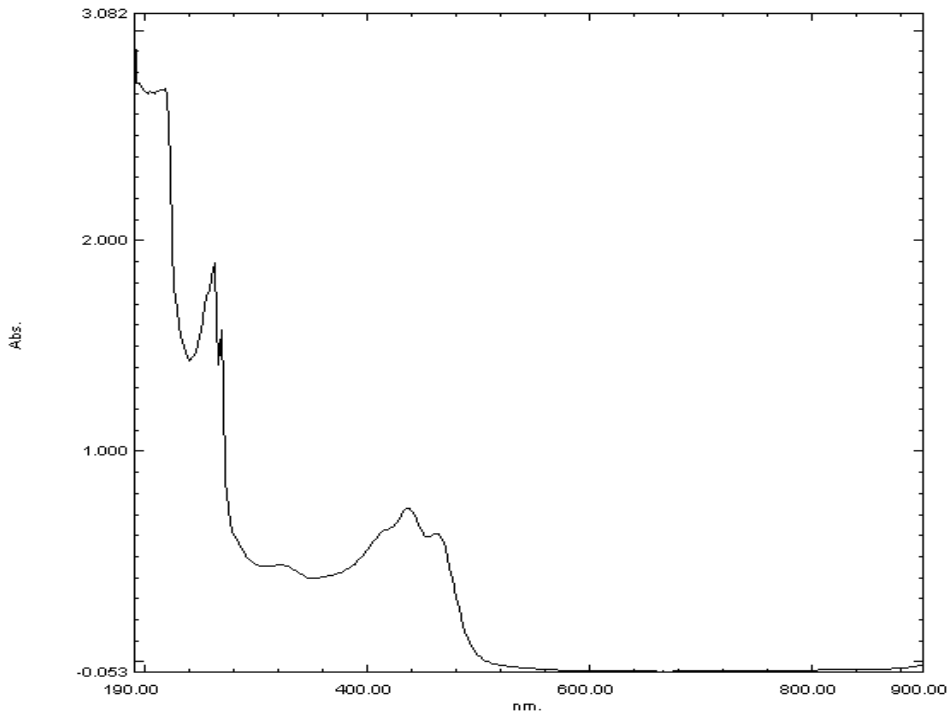

Figure-2: UV spectrophotometry spectra of sigma saffron extract (0.2mg/ml) with 70% v/v ethanol.

