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Review

Distribution, chemical composition and medicinal importance of saffron (*Crocus sativus* L.)

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***Crocus sativus* L. is native to Iran and Greece, and is now cultivated largely in Southern Europe, Tibet and other countries. In India, it is mainly cultivated in Kashmir. *C. sativus* is an important medicinal plant with aphrodisiac, antispasmodic, expectorant, anti-diabetic, anti-inflammatory, antioxidant, anti-depressant, anticancer and anti-tumor activities. Phytochemical investigations of the species have revealed the presence of a number of important carotenoids especially crocetin and its glycosidic forms such as crocin, picrocrocin and safranal. The genetic origin of *C. sativus* is believed to have occurred by auto-triploidy or by allopolyploidy and *Crocus cartwrightianus* is believed to be its most probable ancestor. World over, saffron shows a declining trend in production and productivity due to high labour cost, lack of variability for major economic traits and poor economic returns. This review focuses on the detailed distribution, chemical composition and the medicinal importance of saffron.**

Key words: *Crocus sativus*, crocin, picrocrocin, safranal, medicinal properties.

INTRODUCTION

Crocus sativus L. (Family Iridaceae) commonly known as saffron is distributed primarily in the Mediterranean Region and South Western Asia. The safranal (for ordor), picrocrocin (for taste) and crocin (for pigment) components of this geophyte constituting the spice "saffron'' are localized in the red stigmatic lobes of the flower (Neghbi et al., 1989; Plessner et al., 1989; Fernandez, 2004). The stigmas (20 - 40 mm) are dark red in color and trumpet shaped, serrated or indented at the distal end and may be isolated or joined in pairs or threes at the end of the style, which is white/yellow in color (Figure 1b, c). It is estimated that, approximately 75,000 crocus blossoms or more than 2,00,000 dried stigmas produce just one 1 kg saffron spice and is thus the most expensive spice in the world at around $500/kg and/or $40-50/gram (Fernandez, 2007; Melnyk et al., 2010). The stigmas must be handpicked from the delicate blossoms upon opening to preserve the desirable volatile compounds which easily degrade in the presence of light and oxidizing agents (Rau, 1969; Hill, 2004). As a result, the best saffron is usually sold as whole stigmas (not powdered) in air tight containers so as to preserve its integrity. The high value of saffron in the international market makes it the object of frequent adulteration

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Figure 1. Corm (1a), flower (1b) and stigma (1c) of *Crocus sativus* L.

and fraud by the growers, traders and other stake holders (Fernandez, 2007; Husaini et al., 2010a). The quality and commercial value of saffron is determined by its coloring power, bitter taste and aroma. These three parameters are certified in the international market following the International Organization for Standardization (ISO 1993). The "Saffron Specifications" and "Saffron Test Methods" issued by the Institute of Standard and Industrial Research Organization of Iran (ISIROI) explain the sampling, packing, labeling and methods of testing of saffron. In India, the Bureau of Indian Standards (BIS) is responsible for setting up guidelines for quality standards of saffron (Husaini et al., 2010a).

Saffron is a geophyte herbaceous plant and is propagated vegetatively by corms (underground, compact, bulb-like, starch-storing organs shrouded in a dense mat of parallel fibres called "corm tunic"). A single corm of 10-15 g weight survives for one season, producing at the end of growing season 6-10 "cormlets" that can grow into new plants in the next season (Figure 1a). The plant is a triploid (X=8; 2n=3X= 24), self and out-sterile, mostly male sterile (Mathew, 1977; Ghaffari, 1986; Grilli Caiola, 2005) and is therefore unable to produce seeds. Archeological and historical sources indicate the saffron cultivation as very old dating back to 2500 - 1500 BC, probably originating in Iran, Asia Minor or Greece which later became wide spread in India, China, the Mediterranean Basin and Eastern Europe (Negbi, 1999; Grilli Caiola et al., 2004). The auto-triploid nature and vegetative mode of reproduction of the species renders improvement by conventional breeding very difficult. As the species has spread by vegetative means, it is believed that saffron exists as a single species all over the world.

Recent studies have confirmed that saffron exhibits stable biological traits all over the world and there are no genomic differences (Grilli caiola et al., 2004; Zubor et al., 2004; Fernandez, 2007). The stigmas of saffron have been used from ancient times as a spice in food, as a dye in perfumes and cosmetics preparation and for medicinal purposes (Basker and Negbi, 1983). The present review describes the current status of saffron crop and its medicinal properties so as to have insight interest among young researchers for their possible contributions in promoting this precious crop in the world.

Origin and distribution

The name "saffron" is derived from the Arabic word zafaran which means yellow (Winterhalter and Straubinger, 2000), the ancient Greek called it "Koricos" where as Romans used the term "Crocum". In India, this golden spice is known as "Kum Kum" and "Kesar" in Sanskrit and "Koung" in Kashmiri language. It is believed that saffron is being cultivated for about 3,500 years in Egypt and Middle East and during the Middle Age, saffron crop was extended from Middle East to Europe reaching Great Britain in the 14^{th} Century (Fernandez, 2004). The detailed archaeological and historical records of occurrence and spread of saffron and its allied species have been reviewed by Grilli Caiola (2010). The centre of origin of *C. sativus* according to Vavilov (1951) is the Middle East, while other authors suggest Asia Minor or the South-West Greek Islands as its probable area of origin (Tammaro, 1990). According to Negbi (1999), *C. sativus* was probably selected and domesticated in Crete during the Late Bronze Age.

From here, it spread to India, China and the Middle Eastern countries. From these latter, the Arabs brought saffron to all Mediterranean Europe (Ingram, 1969). Some authors (Alberini, 1990; Winterhalter and Straubinger, 2000) point towards Iran and Kashmir as its origin site from where it has spread to Greek and Roman world. The precise time of introduction of saffron in Kashmir is not known, although evidence from a 12^{th} Century book, "Rajatarangini" written by a Kashmir Poet (kalhana), indicates its presence in Kashmir even before

Table 1. Estimate of saffron world production (Adopted from Gresta et al., 2008).

Country	Area (ha)	Production (Kg)	References
Iran	47,000	160,000	Ehsanzadeh et al., 2004
India	-	8,000-10,000	Fernandez, 2004
Greece	860	4,000-6,000	Fernandez, 2004
Azerbaijan	675	-	Azizbekova and Milyaeva, 1999
Morocco	500	1,000	Ait-Oubahou and El-Otmani, 1999
Spain	200	300-500	Fernandez, 2004
Italy	35	120	NA
France	1	4	Girard and Navarrete, 2005
Turkey	-	10	Thiercelin, 2004
Switzerland	-	0.4	Negbi, 1999

NA - reference not available.

the reign of King Lalitaditya in 750AD (Husaini et al., 2010b). The genetic origin of *C. sativus* is believed to have occurred by auto-triploidy from a wild *Crocus*, probably by fertilization of a diploid unreduced egg cell by a haploid sperm cell or a haploid egg cell by two haploid sperms (Chichiriccò, 1984; Grilli Caiola, 2004, 2005), or by allopolyploidy through the hybridization of *Crocus cartwrightianus* and *Crocus hadriaticus* (Castillo et al., 2005). Brighton (1977) in a kariological study and supported by AFLP analysis (Zubor et al., 2004) suggested that possible ancestors of *C. sativus* are *C. cartwrightianus* or *Crocus thomasii*. Evidences from several other workers suggest *C. cartwrightianus* as the most probable ancestor of *C. sativus* (Mathew, 1999; Brandizzi and Grilli Caiola, 1998; Grilli Caiola et al., 2004).

Saffron is currently being cultivated more or less intensively in Iran, India, Greece, Spain, Italy, Turkey, France, Switzerland, Israel, Pakistan, Azerbaijan, China, Egypt, Japan, Afghanistan, Iraq and recently in Australia (Table 1). While the world's total annual saffron production is estimated at 205t per year, Iran with more than 47,000 ha, of land under saffron cultivation produces 80% (160t) of this total. Khorasan province in Iran alone accounts for 46,000 ha land and 137t of the total production in Iran (Parviz et al., 2004). The traditional cultivated areas in Europe (Spain, Italy and Greece) are showing a severe declining trend while an enormous increase has been registered in Iran in the last 30 years (Skubris, 1990; Fernandez, 2004). In India saffron is exclusively cultivated in Kashmir division of Jammu and Kashmir State.

Locally known as "Koung" and generally grown on uplands (Karewas), this crop covers about 4% of the total cultivated area of the Kashmir valley and produces 5-6t annually (Husaini et al., 2010a, b). Saffron export from India declined from 9.7t (1998-99) to 8.7 tons (2000-01) associated with a decline in spot price of saffron from Rupees (Rs.) 32,936/kg ($ 866) in 1997-98 to Rs.17, 500 ($ 374) in 2004-05 (Nehvi et al., 2007). The total area under this crop and annual production in the state is showing a declining trend over the past more than one decade (Table 2). According to Husaini et al. (2010b), the saffron crop has shown a decrease of 83% in area, 215% in production and 72% in productivity. The major reasons for decline in saffron cultivation and production constraints in the world as well as in J&K state of India are high labour cost, lack of variability for major economic traits, low corm yield, disease susceptibility, low yield of biochemical like safranin, picrocrocin and crocin and above all poor economic returns. The cultivation practices of saffron in Kashmir and the factors responsible for decline in saffron production have been reviewed by Husaini et al. (2010b).

Chemical constituents of saffron

Apart from the primary metabolites such as carbohydrates, minerals, fats and vitamins, the *Crocus sativus* L. contains four major bioactive compounds viz., crocin (Mono-glycosyl polytene esters), crocetin (a natural carotenoid dicarboxylic acid precursor of crocin), picrocrocin (monoterpene glycoside precursor of safranal and product of xeaxanthin degradation) and safranal (Figure 2), all contributing to colour, taste and aroma respectively (Melnyk et al., 2010). According to Sobolev et al. (2014), presence of biologically active compounds such as crocetin, picrocrocin and safranal makes this spice a promising candidate for being a functional food. The hydrophilic carotenoids of saffron which includes crocins constitute about 6-16% of saffron's dry matter depending upon the variety, growing conditions and processing methods (Gregory et al., 2005). The highly water soluble crocins are widely used as a natural food colourant and also act as an antioxidant by quenching free radicals, thus protecting cells and tissues against oxidation (Assimopolou et al., 2005; Soeda et al., 2007; Melnyk et al., 2010). Amongst the other minor components belonging to this class, β-crocetin and γ-

Table 2. Area, production and productivity of saffron in Kashmir, India.

Year	Area (ha)	Production (ton)	Yield/productivity (kg ha^{-1})
1996 - 1997	5707	15.96	2.79
1997 - 1998	NA	NA	NA
1998 - 1999	4116	12.88	3.12
1999 - 2000	3997	7.65	1.91
2000 - 2001	2831	3.59	1.26
2001 - 2002	2880	6.52	2.26
2002 - 2003	2742	5.15	1.87
2003 - 2004	3075	4.83	1.57
2004 - 2005	2989	8.85	2.96
2005 - 2006	2928	4.85	1.65
2006 - 2007	2436	9.13	3.74
2007 - 2008	3110	5.06	1.62

Adopted from Husaini et al. (2010) (Sources: Planning Department J&K Government/Directorate of Agriculture Jammu and Kashmir Divisions/Economic Survey 2008 - 09, J&K Government)
NA: Data not available

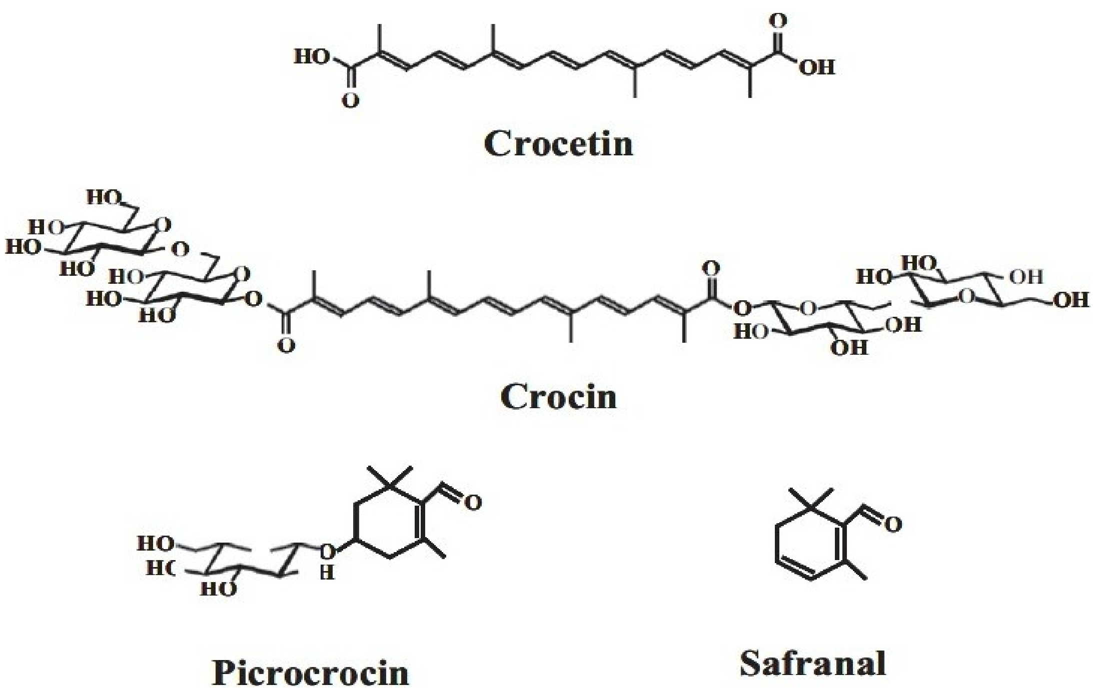

Figure 2. Major chemical constituents of *Crocus sativus* L. (adopted from Gresta et al., 2008).

crocetin, the mono and dimethyl esters of crocetin respectively and mangi-crocin, an unusual xanthone-carotenoid glycosidic conjugate, have also been identified (Sampathu et al., 1984; Ghosal et al., 1989; Fernandez, 2004). The picrocrocin which is the second most abundant component (1-13% of saffrons dry matter) is a colourless glycoside and is considered the main bitter principle of saffron, even though other components, such as flavonoids are also responsible for saffron's bitterness (Alonso et al., 2001; Carmona and Alonoza, 2004). Picrocrocin like other members of the crocin family is derived from the enzymatic degredation of zeaxanthin; in turn, the natural de-glycosylation of picrocrocin gives safranal (Sampathu et al., 1984; Pfander and Schurteberger, 1982) which is the main volatile component of saffron, responsible for the particular aroma of this spice. The safranal represents approximately 30-37% of essential oil and 0.001 to 0.006% of dry matter (Carmona et al., 2007; Maggi et al., 2009). Besides its aromatic potential, safranal has antioxidant potential (Kanakis et al., 2007) and cytotoxic effect on certain cancer cells (Escribano et al., 1996). There are also other typical volatile components of saffron, all possessing the same skeleton of safranal and like this, are considered to derive from picrocrocin (Melnyk et al., 2010), even though the recent discovery of several new glycosides suggests that picrocrocin is not the soluble glycosidic aroma precursor in saffron (Straubinger et al., 1998; Carmona et al., 2006). The extraction and purification protocol for various chemical and volatile constituents of saffron are available in the literature (Tarantilis et al., 1994; Tarantilis and Polissiou, 1997; Lozano et al., 2000, Zareena et al., 2001).

Several minor components have also been isolated from stigmas and other plant parts, mainly petals and corms. Terpenoids such as crocusatins present in stigmas and petals and showing a significant antityrosinase activity, are among the most recovered components (Li and Wu, 2002, 2004). To the same class of substances namely terpenoids, belong several glycosidic derivatives which are considered as the precursors of volatile saffron components alternative to picrocrocin (Straubinger et al., 1997, 1998). Moreover, a series of flavonoids, all glycosidic derivatives of kaempferol, have recently been characterized in the stigmas of saffron; these polyphenols probably concur together with picrocrocin to produce the bitter taste of saffron (Carmona et al., 2007). Other secondary metabolites from *C. sativus* include anthraquinones and an anthocyanin (Saito et al., 1960; Gao et al., 1999), isolated from corms and petals, respectively.

The chemical composition and concentration of various metabolites in saffron vary from one geographical region to other. Several analytical techniques are available to differentiate saffron samples of different origin based on their chemical composition (Zalacain et al., 2005; Zougagh et al., 2006; Maggi et al., 2009, 2011; Yilmaz et al., 2010). Recently, Sobolev et al. (2014) proposed a microwave assisted NMR based analytical protocol for recovery of metabolites showing significant differences among geographically different saffron extracts.

Medicinal importance of saffron

Saffron (*C. sativus* L.) has been cultivated from time immemorial for its stigmas, which not only comprise a highly valued spice but also have various therapeutic uses (Sampathu et al., 1984). It is used mainly as a dye in industry, as a spice in cooking, as a food colorant and as a component of drugs and perfumes (Mathew, 1982; Basker and Negbi, 1983; Behnia et al., 1999). Saffron has been used as a drug to treat various human health conditions such as coughs, stomach disorders, colic, insomnia, chronic uterine hemorrhage, scarlet fever, smallpox, colds, asthma and cardiovascular disorders (Giaccio, 1990; Winterhalter and Straubinger, 2000; Abdullave, 2003). It has been shown that saffron is a protective agent against chromosomal damage (Prem kumar et al., 2001). Saffron can also be used to help clear up sores and to reduce the discomfort of teething infants (Abdullaev and Espinosa- Agurre, 2004).

Among the secondary metabolites present in saffron, the ester derivatives of crocetin, together with safranal, are nowadays the most studied compounds to evaluate their biological activity. Recent data shows that saffron possesses tyrosinase inhibitory (Li and Wu, 2002, 2004), anticonvulsant (Hosseinzadeh and Younesi Hani, 2002), mutagenic (Abdullave and Espinosa-Aguirre, 2004), cytotoxic and antigenotoxic effects (Abdullaev et al., 2003). It has also anti-amyloidogenic activity against Alzheimer's disease (Papandreou et al., 2006); anti-inflammatory (Hosseinzadeh and Younesi, 2002) and blood pressure reducing (Fatehi et al., 2003) effects. Crocin extracts from saffron have been used for the treatment of nervous, cardiovascular and respiratory systems (Abe and Saito, 2000; Abdullaev, 2002). Components of saffron extract have been found to play a role in management of mental disorders and also act as antidepressant agents (Lechtenberg et al., 2008; Basti et al., 2007). It has been found that the treatment with saffron extracts is not associated with sexual dysfunction in humans, a side effect often encountered with antidepressant drugs (Modabbernia et al., 2012; Kashani et al., 2013).

Recently, saffron extract has been successfully tested as an anticancer agent (Abdullaev, 2007) as well as against mental disorders. Cancer chemopreventive and tumoricidal properties of saffron extracts have been reported by several workers following *in vitro* and *in vivo* assays with encouraging results (Abdullaev, 2002; Ochiai et al., 2004; Ahmad et al., 2005; Hosseinzadeh et al., 2005; Magesh et al., 2006). According to Hartwell (1982) saffron extracts have been used against different kinds of tumors and cancers (liver, spleen, kidney, stomach and uterus tumors) in ancient times. Anti-tumor effect of saffron on different malignant cells in some model animals has also been reported (Abdullaev, 2004). Very recently, De Monte et al. (2014) studied the inhibitory activities of two natural components of *C. sativus* viz. crocin and safranal as well as some newly designed components derived from chemical modifications of safranal on the human monoamine oxidases (hMAO-A and hMAO-B- the two important enzymes which are targets for the treatment of neuropsychiatric and neurodegenerative diseases). Their results confirmed crocin as a relatively weak inhibitor of hMAO, while as safranal was not found as hMAO inhibitor indicating that hMAO are probably not targets of crocin and safranal. The designed chemical derivatives of safranal, however, displayed much improved inhibitory activities against both hMAO enzymes. The synthetic derivatives could thus

Table 3. Major biological functions attributed to saffron and its chemical constituents.

Activity	Saffron constituents tested	Reference
Prevention of gastric disorder	Saffron crude extract Ethanolic saffron extract	Inoue et al. (2005) Kianbakht and Mozaffari (2009).
Prevention of stomach ulcer	Crocin	Xu et al. (2009)
Digestion enhancement	Aqueous saffron extract	Nabavizadeh et al. (2009)
Anticancer function and cytotoxic effects on tumor cells	Ethanolic saffron extract Crocin, crocetin, safranal and picrocrocin	Tavakkol-Afshari et al (2008) Escribano et al. (1996) Garcia-Olmo et al. (1999) Abdullaev (2002) Mousavi et al. (2009)
Tumor inhibition	Crocin Saffron Crocetin	Garcia-Olmo et al. (1999) Salomi et al. (1991) Wang et al. (1996)
Cardiovascular health promotion Anti-atherosclerosis	Crocin Crocetin	He et al. (2005) He et al. (2007) Sheng et al. (2006)
Prevention of insulin resistance	Crocetin	Xi et al. (2007)
Anti-depression activities	Capsulated ethanolic saffron extract Saffron petal extract Aqueous and ethanolic saffron extract	Akhondzadeh et al. (2005) Akhondzadeh et al. (2007) Moshiri et al. (2006) Hosseinzadeh et al. (2004)
Premenstrual syndrome (PMS) treatment	Capsulated ethanolic saffron extract	Agha-Hosseini et al. (2008)
Detrimental health effects Nausea, vomiting, uterus bleeding, abortion	Saffron	Schimidt et al. (2007) Lucas et al. (2001)

Modified and adopted from Melnyk et al. (2010).

prove novel hMAO inhibitors for clinical management of psychiatric and neurodegenerative disorders. A detailed review by Melnyk et al. (2010) highlights major biological functions attributed to different constituents of saffron (Table 3).

PROSPECTS OF GENETIC IMPROVEMENT

Saffron's high price is due to the much direct labour required for its cultivation, harvesting and handling (Fernandez, 2004). In recent past, saffron cultivation and production has shown a declining trend due to high labour cost, low economic returns and very short and laborious flower picking period. There is an urgent need for increasing saffron production and quality to cope with an increasing demand of this spice in the market. This can be achieved by putting in more efforts on genetic improvement of the crop with main focus on producing more flowers per plant, flowers with a higher number of stigmas, increasing stigmas size or stigmas with an increased amount of dye and aroma (Fernandez, 2004). Due to triploid behavior, the chances of crop improvement by conventional methods like hybridization are not possible (Basker and Negbi, 1983). The utilization of spontaneous variability in the natural population which is due to genetic and environmental factors and other non-conventional approaches of crop improvement offer tremendous scope for saffron improvement (Estilai, 1978; Dhar et al., 1988; Nehvi, 2003). Several workers in recent years have attempted mutation breeding technique for induction of genetic variability followed by selection and multiplication of mutant clones (Nehvi et al., 2010). The use of mutagenesis could enhance the genetic base of the crop species so as to offer chances of selection for elite genotypes particularly with respect to stigmatic and corm characteristics. The preliminary results of induced genetic variability through gamma irradiation and induction of polyploidy through colchinization are, however, not satisfactory and probably would require further work (Akhund-Zade and Mazaferova, 1975; Khan, 2004; Zaffar et al., 2004). Creation of saffron germplasm banks, improvement in cultivation techniques, supply of quality plant material and development of quality evaluation methods are some important measures to be considered while dealing with enhancing saffron productivity and its usage.

CONCLUSION

Saffron cultivation has been neglected for many decades by farmers, who have relegated it to adverse soil and climate conditions, and by research, which has led to a lack of innovation. The chemical profile of saffron and its medicinal and cultural properties makes it a golden spice and there is an urgent need of attention on scientific community to focus their research on genetic improvement of this precious crop. Increase in saffron production and quality can be achieved by means of plants with more flowers per plant, flowers with a higher number of stigmas, increased stigma size or stigmas with a greater amount of dye and aroma. The sterility of saffron limits the application of conventional breeding approaches for its further improvement. Induced variability by physical and chemical mutagens can be considered a viable option for improvement in saffron yield, even if no significant results have been achieved as yet.

Conflict of Interests

The author(s) have declared that there is no conflict of interests.

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