Tariq Aftab
Khalid Rehman Hakeem *Editors*

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Editors
Tariq Aftab
Department of Botany
Aligarh Muslim University
Aligarh, India

Khalid Rehman Hakeem
Department of Biological Sciences
King Abdulaziz University
Jeddah, Saudi Arabia

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Chapter 13
Saffron: A Therapeutic and Prophylactic Nutrition for Human Population

M. H. Khan, B. A. Alie, A. M. I. Qureshi, G. H. Mir, N. A. Dar, Shahid Qayoom, Tauseef Ali, S. A. Dar, A. A. Lone, Z. A. Dar, M. Ahmad, M. A. Bhat, and F. A. Sheikh

13.1 Introduction

Saffron (*Crocus sativus* L.) a perennial herb belonging to Iris family Iridaceae is cultivated from the times immemorial. The primary illustration dates back from 1600 to 1700 BC that was established on a frieze of Minos Fort in Crete, unfolding records plucking saffron (Algrech 2001). Vavilov indicated that it originated in the Middle East, even though other authors proposed Central Asia as well as islands of Southwest Greece (Tammaro 1989), and from these areas, its spread was found in India, China and Middle East countries. The cultivation of saffron differs from one region to another depending on various factors like cultural practices and climatic and edaphic conditions of that particular area. The average water requirement of the spice varies from 400 to 600 mm/year. Saffron is economically much more viable spice since it fetches higher price, both at national and international market, and presents a strong added value. Besides economic importance, it also plays a significant role in environmental and social domain. The harvesting of crop mobilizes a large workers especially females. For production of 1 kg of saffron, 150,000–170,000 flowers are required and about 400 working hours (Mzabri et al. 2019). This chapter will describe the importance of saffron in therapeutic use, role of phytochemicals generally found in this spice and other uses that give it specific popularity particularly in the field of medical sciences where there are not many available reports authenticating the use of this spice.

M. H. Khan · B. A. Alie · A. M. I. Qureshi (✉) · G. H. Mir · N. A. Dar · S. Qayoom · T. Ali · S. A. Dar · A. A. Lone · Z. A. Dar · M. Ahmad · M. A. Bhat · F. A. Sheikh
Advanced Research Station for Saffron and Seed Spices, SKUAST-Kashmir, Pampore, India

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13.2 Genetic Origin

The information regarding saffron ancestors is not yet clear; however, botanical studies revealed that *C. sativus* is a mutant population of *C. cartwrightianus*. *Crocus sativus* and *Crocus cartwrightianus* are morphologically indistinguishable; *Crocus sativus* flowers are twice as broad as those of *Crocus cartwrightianus* (Gresta et al. 2008). Grilli et al. (2001) conducted RAPD (random amplification of polymorphic DNA) investigation to scan the putative predecessors of *Crocus sativus* and reported that *Crocus cartwrightianus* is the nearest related species to *Crocus sativus*, trailed by *Crocus thomasii*. AFLP investigation (enhanced DNA section length polymorphisms) affirmed that the quantitative and subjective DNA attributes of both *Crocus cartwrightianus* and *Crocus thomasii* species are compatible with those of *Crocus sativus* (Zubor et al. 2004).

13.2.1 Botanical Description

Saffron (*C. sativus* L) is one of the exceptional plants in the world which belongs to the family Iridaceae. There are around 80 members of this family worldwide (Hagh-Nazari and Keifi 2007). This herbaceous plant (Fig. 13.1a) attains a height of 10 and 25 cm which arises from its corm. The corm is of variable size and is somewhat subovoid in shape. It has a large foundation and is surrounded by various dense spathes. The apical buds of each mother corm produce one to two flower-bearing corms and numerous small corms (non-flower-bearing) from lateral buds (Grilli et al. 2001). There are two types of roots found in saffron, viz. fibrous roots which arise at the base of mother corm and contractile roots which are formed at the base of lateral buds (Zubor et al. 2004) (Fig. 13.1b). Each bud produces 5–11 leaves (Fig. 13.1c), which are very thin, attaining a size of 1.5–2.5 mm of dark green colour. The leaves are 20–60 cm long with a whitish band in the internal part and a rib outwardly.

Fig. 13.1 *Crocus sativus* plant morphology: (**a**) saffron plant; (**b**) types of roots in saffron; (**c**) saffron leaves; (**d**) saffron flower

At the beginning of autumn and towards the end of September, the flowers of saffron begin to appear which are purplish and composed of six petals which are joined at the cylindrical long tube that emerges from the upper portion of the ovary (Fig. 13.1c). The flowers at the exterior end are sheltered by whitish membranous bracts. The ovary is inferior from which a thin style, 9–10 cm long, arises which in turn consists of a single stigma that is composed of three stigmas of intense red colour which are the most important economical part of the plant (Molina et al. 2003).

13.3 Main Phytochemical Components of Saffron

Chemical analysis of saffron reported presence of about 150 volatile and non-volatile compounds. Until now less than 50 constituents have been recognized (Winterhalter and Straubinger 2000). The three major biologically active compounds are crocin, a carotenoid pigment accountable for the spice's yellow-orange colour; picrocrocin, which provides flavour and bitter taste for the saffron; and safranal, which produces aroma to saffron (Fig. 13.2).

Crocin ($C_{44}H_{64}O_{24}$) is a naturally occurring carotenoid which is easily soluble in water. Compared with other carotenoids, it has a broader application as a dye in foods and medicines, owing to its high solubility. Picrocrocin ($C_{16}H_{26}O_7$) is the principal element that makes bitter taste of saffron which can be solidified by hydrolysis (Moghaddasi 2010). Safranal ($C_{10}H_{14}O$) is responsible for the flavour and aroma of

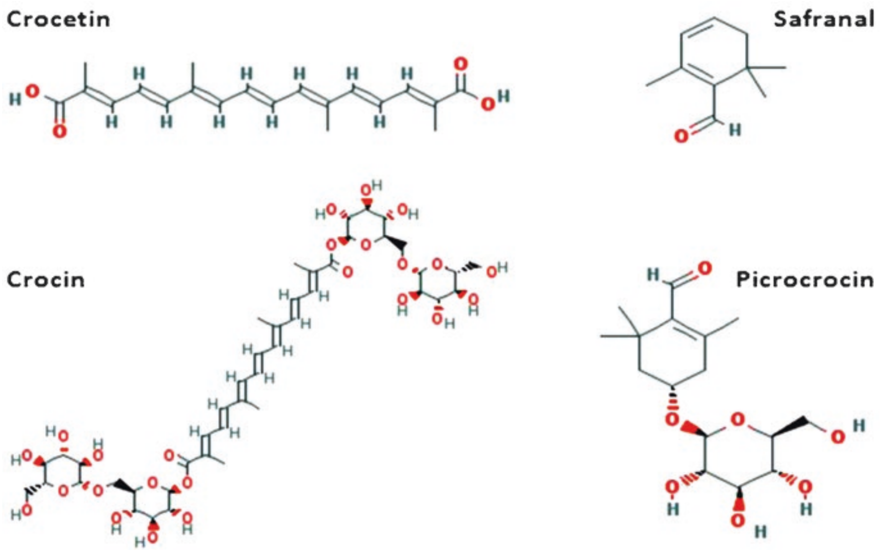

Fig. 13.2 The main biologically active compounds of saffron

the spice, and its concentration depends on the post-harvest handling of the saffron (Ait Oubahou 2009). Besides these three compounds, the major constituents in saffron are anthocyanins, flavonoids (such as kaempferol), vitamins, amino acids, proteins, starch, mineral matter and gums (Winterhalter and Straubinger 2000). It also contains many non-volatile active components many of which are carotenoids including zeaxanthin, lycopene and various α- and β-carotenes. There are 34 volatile components in saffron, which include terpenes, terpene alcohols and their esters (Liakopulou and Kyriakides 2002).

The three compounds (crocin, picrocrocin and safranal) determine the quality of saffron and provide the colour, taste and aroma of stigmas. The concentration of these compounds depends on the environment and cultural practices (Gresta et al. 2009). The post-harvest techniques like drying, extraction and stigma analysis determine the chemical composition of saffron samples (Kanakis et al. 2004; Tarantilis et al. 1995; Zareena et al. 2001). The quality of saffron is regulated by ISO 3632 standards which are directed at standardizing the classification of saffron globally and are updated every 3 years.

13.4 Nutritional Facts

Saffron is rich in vital minerals like zinc, magnesium, copper, calcium, potassium, iron, selenium and manganese. Besides these essential minerals, it also contains many important vitamins (Table 13.1).

13.5 Ethnomedical Importance of Saffron

Research's showed that saffron was used by Assyrians and Babylonians to treat dyspnoea, head problems, menstruation, delivery and painful urination. The earliest evidence of medicinal usage of saffron is in the Assurbanipal library, in inscriptions from the twelfth century BC (Mousavi and Bathaie 2011). It is used in Ayurveda to treat chronic illnesses such as asthma and arthritis. Also, it is used to treat colds and cough. Ayurvedic, saffron-containing drugs are used to cure acne and multiple skin disorders. Ancient texts have shown that the herb is useful as an aphrodisiac; therefore, it stimulates reproductive system. The stigmas of saffron are usually used as folk medicine as well as traditional medicine in India and China, respectively (Bhandari 2015). Saffron was a royal colourant in ancient Greece and was used as a perfume in saloons, courts, theatres and bathrooms. Besides herbal cure properties of crocus, many great personalities like Hippocrates (5–4th century BC), Erasistratus (2nd–3rd century BC), Diokles (3rd century BC) and Dioscorides (1st century AD) used this golden spice for therapeutic purposes like treating eye diseases (painful eye, corneal disease and cataract, purulent eye infection), earache, toothache, ulcers (skin, mouth, genitalia) and erysipelas; they believed that it has styptic and sedative features (Mousavi and Bathaie 2011).

Table 13.1 Saffron (*Crocus sativus*), nutritional value per 100 g

Principle	Nutrient value
Energy	310 Kcal
Carbohydrates	65.37 g
Protein	11.43 g
Total fat	5.85 g
Cholesterol	0 mg
Dietary fibre	3.9 g
Vitamins	
Folates	93 μg
Niacin	1.46 mg
Pyridoxine	1.010 mg
Riboflavin	0.267 mg
Vitamin A	530 IU
Vitamin C	80.8 mg
Electrolytes	
Sodium	Sodium 148 mg
Potassium	Potassium 1724 mg
Minerals	
Calcium	111 mg
Copper	0.328 mg
Iron	11.10 mg
Magnesium	264 mg
Manganese	28.408 mg
Phosphorus	252 mg
Selenium	5.6 μ g
Zinc	1.09 mg

13.6 Biological Activities of Saffron

The biochemical components of saffron particularly crocin have many therapeutic properties such as antitumour, antioxidant, anxiolytic, neuronal protective and anti-ischaemic and act as a protectant against various DNA damage activities (Mohajeri et al. 2010). These components are possible anticancer agents as well as hypolipidaemic and antioxidant agents, protect the brain against unnecessary oxidative stress, protect the ischaemic heart, help to mitigate neurological deficiencies, have important anti-proliferation effects on human prostate and colorectal cancer cells, have aphrodisiac function, are immunomodulatory, improve inhibition of Dalton's lymphoma, are helpful in diabetic neuropathy treatment, affect glucose uptake and insulin sensitivity and have many more activities. The sub-component of crocin i.e. crocetin, enhances alveolar oxygen transport and increases pulmonary oxygenation, obstructs skin tumour promotion and avoids oxidative damage, has cardiovascular protective effects, improves hypertension-mediated acetylcholine-induced vascular relaxation, acts as a powerful antitumour agent, inhibits angiogenesis mediated by the endothelial growth factor, etc. (Agnihotri and Aperito 2015).

Crocetin has several positive effects although some work to the contrary has shown that crocetin may be a teratogenic agent. Crocetin's high dose induced miscarriage which may be dangerous (Mohajeri et al. 2007). Crocin has a lot of biological activity; even so crocin (200 mg/kg, i.p.) has not shown anticonvulsants which means crocin is a good antidepressant (Ahmad et al. 2012). Crocin has shown numerous pharmacological effects on the nervous system, such as anti-anxiety function, therapeutic effects, aphrodisiac powers and thinking and performance improvement (Alavizadeh and Hosseinzadeh 2014). Saffron slightly reduces some haematological parameters like red blood cells, haemoglobin, haematocrits and platelets. It improved sodium, nitrogen urea in the blood, creatinine, etc. (Modaghegha et al. 2008).

13.7 Possible Mechanism of Action of Saffron and Its Ingredient in Disease Prevention

The stigma of the saffron is blend of different segments, and such constituents have therapeutic significance in the well-being of human beings occurring through different natural pathways. The accurate component by which saffron and its constituents exhibit the remedial job in disease anticipation is yet to be completely explained. Lab-based exploration has uncovered that saffron constituents through the action of different compounds are engaged with free radical detoxification. Additionally, these segments diminish the lipid peroxidation and upgrade the cell reinforcement status. The ethanolic fraction of stigma demonstrated the most noteworthy cancer prevention action that may be perceived because of the presence of different phenolics and flavonoids (Amin et al. 2014). Other test information advocates that saffron helps in the decrease of irritation through the hindrance of cyclooxygenase protein action. Saffron eases neuropathic torment by means of decrease of pro-inflammatory cytokines, cancer prevention agent and apoptotic pathways (Xu et al. 2009), and in vitro examination has uncovered that crocin has double inhibitory action against COX-1 and COX-2 enzymes (La Barre 1961). Saffron additionally shows a significant role in the tumour avoidance, and a few discoveries advocate that saffron and its constituents initiate apoptosis or change the proportion of bcl2/bax lastly restraining the turn of events and movement of tumour.

13.8 Pharmacological and Prophylactic Activities of Saffron

Saffron is known for a very huge number of potential uses and activities. The pharmacological properties of saffron components, like safranal, crocin and crocetin, are due to their chemical structure. The studies based on in vitro experiments showed the most important pharmaco-active properties of saffron that appeared in the Chemical Abstracts between 1925 and 1999, however, these old information were observational and their medical significance remains doubtful. Safranal was proposed as one of the gastrointestinal chemical function modifiers. It can stimulate appetite and prevent gastrointestinal atonia through this action (Giaccio 2004). Saffron has also shown therapeutic action on the female genitals. Safranal may be helpful in the treatment of respiratory, mostly chronic bronchitis, with respect to its major components. Owing to its wide dissemination to the lungs, safranal sedates coughing, functioning as an anaesthetic on the alveoli's vagal nerves (Lequerc 1973). Crocin has been suggested for painful relief of dysmenorrhoea because it may reduce uterine contractions. Picrocrocin tends to have a sedative effect on lumbar pressure and spasms (Frank 1961). However, crocetin has been linked to the most extraordinary results of saffron, as it is a material capable of raising oxygen transport speed and diffusivity, both in vivo and in vitro. This ability to carry oxygen makes crocetin a useful therapeutic candidate in different situations, such as atherosclerosis, alveolar hypoxia, haemorrhages, fermentation and cell reproduction. The detailed pharmacological and possible therapeutic applications of saffron are given under the following heads.

13.8.1 Antidepressant and Anxiolytic Properties

Aqueous and ethanol extracts of saffron stigmas have been found to have antidepressant effects in mice, primarily attributed to saffron and crocin acting by inhibiting dopamine, norepinephrine and serotonin intake (Karimi 2001). These results were further confirmed by Wang (2010) who demonstrated behavioural models that revealed antidepressant effect of aqueous saffron extract is attributable to crocetin. It has been shown by Pitsikas (2008) that crocin @ 50 mg/kg has a positive effect on mice behaviour while having anxiolytic effect in rats. Hosseinzadeh and Noraei (2009) showed that safranal specifically can bind to some subtypes of benzodiazepines (BZ1, BZ2 and BZ3).

In clinical trials, 20–30 mg of saffron extract was used for the treatment of mild to moderate depression and was compared with chemically synthesized molecules, such as fluoxetine and imipramine (Akhondzadeh 2005; Hosseinzadeh et al. 2012a; Noorbala 2005). The comparative evaluation showed that saffron was similarly successful in mild to moderate depression (antidepressant action) and epilepsy (anticonvulsant action) without inducing its side effects as chemically synthesized medicines. However, clinical trials have not been conducted on dose-related toxicity and adverse effects of saffron extract use as an alternative in the treatment of depression (Alavizadeh and Hosseinzadeh 2014). Hosseinzadeh et al. (2012a) studied saffron and its effect on recognition and spatial memory after chronic cerebral hypoperfusion in Wistar rats. Their study revealed that saffron extract and crocin improve spatial cognitive abilities following chronic cerebral hypoperfusion and the effect may be associated with these antioxidant compounds (Hosseinzadeh et al. 2012a). It has been reported that saffron and its components possess antidepressant and anxiolytic effects (Maes et al. 2011).

Depression is characterized by a reduction in key antioxidants such as vitamin E and zinc and increased oxidative stress and production of ROS (reactive oxygen species) (Hannestad et al. 2011). Increased amounts of inflammatory cytokines such as tumour necrosis factor-α (TNF-α), beta-IL-1 (IL-β) and interleukin-6 (IL-6) induce severe depressive disorder (Akhondzadeh et al. 2004). Saffron has antioxidant, anti-inflammatory, serotonergic, hypothalamic-pituitary-adrenal (HPA) axis-modulating and neuroprotective effects, making it a strong choice for depression treatment (Asdaq and Inamdar 2010a). The main saffron metabolites – crocin, crocetin and safranal – serve as strong antioxidants. In animal studies the components of saffron were effective in increasing the levels of antioxidant enzymes (Wang et al. 2012) and also inhibited the generation of reactive oxygen species resulting in protection against oxidative stress (Rios et al. 1998). Crocin inhibits the take-up of dopamine and norepinephrine. Safranal impacts serotonin intake (Modabbernia et al. 2012). Saffron has been shown to be successful in managing erectile dysfunction associated with fluoxetine in male patients (Kashani et al. 2013) as well as in the treatment of sexual dysfunction induced by fluoxetine including lubrication, arousal and pain (Akhondzadeh et al. 2010). Saffron's safety and efficacy has been assessed for the treatment of disorders such as anxiety, obsessive-compulsive disorder and Alzheimer's disease in mild to moderate form. It inhibits aggregation and deposition of amyloid β in human brain (Maggi et al. 2011).

13.8.2 Radical Scavenging and Antioxidant Activity of Saffron

Crocetin, crocin, safranal, phenolic and flavonoid compounds from dried *Crocus sativus* L. has important intracellular free radical scavenging behaviours and defend cells and tissues from oxidation (Amin et al. 2011). It is considered that free radical scavenging activity involves anti-ageing, anti-inflammatory, anti-carcinogenic, anti-depressant, anxiolytic, aphrodisiac and also memory-enhancing properties (Asdaq and Inamdar 2010a). The phenolic substance and movement of ethanolic concentrate of saffron was higher when contrasted with the fluid concentrate (Shen and Qian 2006). The water/methanol (50:50, v/v) concentrate of *C. sativus* marks of disgrace displayed great cell reinforcement properties. The concentrate restrained Abeta fibrillogenesis in human cerebrum. Saffron had defensive impact against hyperlipidaemic appearance in liver tissue. Liver tissue which might be because of abatement in the raised lipid levels and oxidative radicals during hyperlipidaemia with enlargement of cell reinforcement exercises (Hosseinzadeh and Sadeghnia 2005). The cardio-defensive impact of crocetin is accounted for to be identified with tweak of endogenous cancer prevention agent enzymatic exercises (Farahmand et al. 2013). Crocetin treatment was successful in diminishing the substance of lipid peroxidation (LPO). An expansion in GSHP-x (glutathione peroxidase) and SOD (superoxide dismutase) action in cardiovascular hypertrophy was additionally watched. Defensive impact of safranal, a monoterpene aldehyde, on various markers of oxidative harm in hippocampal tissue from ischaemic rodents has been accounted for (Rahmani et al. 2017). It could fill in as a powerful possibility to smother age-instigated harm by securing against oxidative pressure and expanding cell reinforcement safeguards (Baba et al. 2015).

The imbalance between the production of reactive oxygen species (ROS) and the level of antioxidants is closely linked to disease pathogenesis. Improving the level of antioxidants or decreasing the level of reactive species is maintained through the antioxidant properties of plants or their derivatives. Natural products or medicinal plant derivatives typically comprise specific components like flavonoids that display a crucial function as antioxidants and free scavenging operation radicals. Numerous in vivo and in vitro studies have shown that *Crocus sativus* has important antioxidant activity (Table 13.2) (Karimi et al. 2010).

Saffron antioxidant activity was observed in the stigma extract, and such studies showed role in reducing chlorophyll injury, lipid peroxidation and protein oxidation (Assimopoulou et al. 2005). Similarly, other findings have confirmed that saffron stigma contains superior antioxidant activity (Goli et al. 2012). Previous findings have shown that active and inactive constituents of saffron extract have high antioxidant activity (Asdaq and Inamdar 2010b) which has been shown in saffron petal extract (Makhlouf et al. 2011). Another study has shown that saffron component such as crocin has high antioxidant activity (Ochiai et al. 2004). Lebanon-based finding showed that saffron significantly reduced lipid peroxidation as well as increased superoxide dismutase activity compared to control group (Papandreou et al. 2006). Crocin, a saffron constituent, showed a role in lipid peroxidation inhibition and restored SOD activity (Sheng et al. 2006), and *Crocus sativus* stigmas contain more antioxidant activity than tomatoes and carrots.

13.9 Saffron's Effect on Hyperlipidaemia and Hypertension

In several human and animal studies, crocin has been reported to be an effective hypolipidaemic agent. Crocin decreased cholesterol levels in hyperlipidaemic rats by feeding excessive cholesterol for 2 months (He et al. 2005). In another research, crocin was found to have significant triglyceridemic and cholesterolemic reduction effects in coils with coronary artery disease (He et al. 2007). The study has verified that crocetin can lower serum, total cholesterol and malondialdehyde levels and prevent nitric oxide reduction in the serum of hyperlipidaemic-diet quails (Joshi et al. 2012). Sheng et al. (He et al. 2005) indicated in the elucidation of crocin's hypolipidaemic mechanism that crocin inhibited the absorption of dietary fat and cholesterol. They stated that this inhibition was very much correlated with fat hydrolysis. Moreover, the adjusted fat-balance approach showed that crocin improved excretion of faecal fat and cholesterol in rats, but had no influence on bile acid removal. Data from the in situ loop method and enzyme assay showed that crocin could not directly inhibit cholesterol absorption from rat jejunum, but could selectively block the pancreatic lipase activity as a competitive inhibitor. These find-

Table 13.2 Pharmacological activities of saffron and its constituents

Aim of study	Biological activity	Finding/outcome	References
Evaluation of antioxidant activity of stigma extract	Antioxidant	Saffron stigma showed antioxidant activity	Kanakis et al. (2004)
Measurement of antioxidant	Antioxidant	Antioxidant activity has been observed	Amin et al. (2014)
Effects of crocin and safranal on local inflammation	Anti-inflammatory	Study finding reported that crocin and safranal showed role in the suppression of inflammatory pain responses and decreased the number of neutrophils	Karimi (2001)
Anti-inflammatory effects of crocin	Anti-inflammatory	Crocin, a constituent, showed anti-inflammatory effects and modulates inflammatory processes	Gresta et al. (2008)
C. sativus extract tested against bacteria	Antibacterial	Strong activity of *C. sativus* extract against bacteria and fungi was noted	Wang (2010)
Evaluation of protective effects of extract against hepatotoxicity	Hepatoprotective	Finding demonstrated that petals ameliorate acute liver injury	Akhondzadeh (2005)
Effect of safranal against nephrotoxicity	Protective effect against nephrotoxicity	Safranal has a protective effect against nephrotoxicity	Maes et al. (2011)
Cardioprotective effect of saffron and safranal	Cardioprotective	Result revealed that myocardial injury preserved nearly normal tissue architecture with saffron or safranal pretreatment	Akhondzadeh et al. (2004)
Inhibitory action on AChE via saffron extract and its constituents	Inhibitory action on AChE	Result indicated that saffron extract showed moderate AChE inhibitory activity	Maggi et al. (2011)
Saffron, crocin and safranal effects on the blood levels of fasting glucose, HbA1c and liver/kidney function tests	Anti-hyperglycaemic	Result demonstrated that saffron extract, crocin and safranal significantly reduced the fasting blood glucose levels but significantly increased the blood insulin levels in the diabetic rats compared with the control diabetic rats	Hosseinzadeh and Sadeghnia (2005)
Effects of saffron and crocin on body weight, food intake and blood leptin levels	Anti-obesity and anorectic	Result concluded that saffron has anti-obesity and anorectic effects and lowered leptin levels	Baba et al. (2015)
Evaluation of anti-obesity effects of saffron and crocin	Anti-obesity	Result showed that saffron extract significantly decreased food consumption in obese rats. Furthermore, crocin showed a significant decrease on rate of body weight gain in rats	Karimi et al. (2010)

(continued)

Table 13.2 (continued)

Aim of study	Biological activity	Finding/outcome	References
Aphrodisiac activities of stigma and safranal and crocin	Aphrodisiac activities	The results revealed that saffron extract and its constituents show aphrodisiac activity	Assimopoulou et al. (2005)
Evaluation of anxiolytic and hypnotic effect of saffron extract, crocin and safranal	Anxiolytic properties	Results confirmed safranal at higher doses demonstrated anxiolytic effects whereas crocin did not show anxiolytic properties	Asdaq and Inamdar (2010b)
Effects of saffron petal extract on blood parameters and the immune system	Immuno-stimulatory	Saffron petal extract use causes an increase in antibody response	Ochiai et al. (2004)
Evaluation of anticonvulsant of safranal and crocin	Anticonvulsant	Finding confirmed that safranal reduced the seizure duration and delayed the onset of tonic convulsions	Sheng et al. (2006)

ings suggest that crocin has lipid-degrading properties by inhibiting pancreatic lipase, resulting in fat and cholesterol malabsorption (He et al. 2005).

Hypertension is the common cardiovascular disease and is a major public health disorder in both developed and developing countries. Saffron produces a crocetin chemical that reduces blood pressure (Imenshahidi et al. 2013a). Researchers study the effects of chronic exposure to saffron stigma aqueous extract on normotensive blood pressure and deoxycorticosterone acetate (DOCA)-salt-induced hypertensive rats (Milajerdi et al. 2015). They conclude that in chronic application, the aqueous saffron extract has an antihypertensive and normalizing effect on blood pressure (Milajerdi et al. 2015). Saffron extract and its components, mainly crocin and safranal, have some modulating characteristics of the blood pressure. Nonetheless, further research need to be performed to identify successful dosage and action mechanisms (Rahmani and Aldebasi 2016).

13.10 Antitumour Activity

It is well established that medicinal plants have a therapeutic function in the treatment of various diseases, including tumour (Nair et al. 1991). Saffron and its active constituents play a significant role in the prevention of tumour growth and progression (Table 13.2). Numerous studies focused on animal models in this regard indicated that saffron plays a part in the prevention of various forms of tumour. Oral administration of saffron extract reveals improved lifespan of sarcoma-180-, Ehrlich ascites carcinoma- and Dalton's lymphoma ascites tumour-bearing mice (Magesh et al. 2006). Later studies have shown that crocetin, a saffron element, intensively reversed the pathological modifications found in cancer animals (Feizzadeh et al. 2008), and other reports have suggested that saffron aqueous extract has inhibitory effects on the development of both transitional cell carcinoma and regular cell lines (Salomi et al. 1991a). Anti-proliferative effects of saffron extract and individual constituents such as crocin were tested on different malignant and non-malignant cell lines of the prostate cancer. Based on these results, crocin decreased proliferation of all malignant cells, whereas non-malignant cells were not affected at all (Aung et al. 2007a). Furthermore, another experiment to explore the chemopreventive influence of aqueous saffron was conducted. The findings of the studies showed that saffron ingestion prevented the development of skin papillomas and simultaneously decreased their size in animals (Wang et al. 1991). In addition, the function of saffron in inducing cytotoxic and apoptotic effects in the lung cancer cells was examined. Results of the study revealed that proliferation of these cells decreased in a dose- and time-dependent manner after saffron treatment (Sun et al. 2013). Crocin inhibited both the weight of the tumour and the size of xenografts in nude mice (Table 13.3). In addition to this, expression of Bcl-2 was inhibited and the expression of Bax was increased in xenografts (Bakshi et al. 2010).

13.11 Chemopreventive Role of Saffron

Crocetin is the primary metabolite in crocins. It inhibits invasiveness of breast cancer cells of MDA-MB-231 by downsetting the expression of metalloproteinase (Bakshi et al. 2010). Dimethylcrocetine, a saffron chemopreventive drug, blocked tumour development by blocking associations between DNA and proteins (Zhang et al. 2013). Saffron's chemopreventive function may be traced to numerous phytochemicals such as terpenes, flavonoids, anthocyanins and carotenoids present in stigma that are reported to have anti-inflammatory, radio-protective, anti-carcinogenic and antitumour properties. It also prevents both DNA and RNA synthesis in HeLa cells originating from a cervical epithelioid carcinoma (Tanaka et al. 2012). Initiation/promotion of skin tumours induced by 7,12-dimethylbenz[a]anthracene (DMBA) in mice is inhibited by the saffron extract (Gutheil et al. 2012). Saffron induced apoptosis in concentration-dependent mode in A549 cells. It can be regarded as a successful chemotherapy agent against lung cancer (Molnar et al. 2000). Alone the crocin and DNA vaccine have been used as antitumour agents in different treatments (Chryssanthi et al. 2011). The dose-dependent inhibition of gastric cancer was observed in rats treated with the aqueous extract of saffron (Nair et al. 1995) and against hepatic cancer by apoptosis induction, oxidative reduction, destruction of inflammatory markers and cell proliferation (Abdullaev and Frenkel 1992; Salomi et al. 1991b). The function of carotenoids in cancer prevention has been widely documented by controlling cancerous growth via multiple mechanisms such as control of cell development, enhancement of cell differentiation, metabolic modulation of carcinogens, immune modulation, stimulation of cell-to-cell gap junction contact, impediment of growth factor signalling

Table 13.3 Antitumour activity of saffron and its ingredients

Aim of study	Tumour/cell type	Finding	References
Antitumour activity of saffron	Sarcoma-180, Ehrlich ascites carcinoma, and Dalton's lymphoma	Study finding demonstrated that oral administration of extract increased the lifespan of S-180-, EAC-, DLA tumour-bearing mice	Imenshahidi et al. (2013a)
Cytotoxic effect of extract of saffron	Transitional cell carcinoma	Study concluded that saffron extract has inhibitory effects on the growth of both TCC and normal cell lines	Rahmani and Aldebasi (2016)
Anti-proliferative effects of *Crocus sativus* extract and crocin	Colorectal cancer	Data from this study demonstrated that *Crocus sativus* extract and crocin significantly inhibited the growth of colorectal cancer cells	Magesh et al. (2006)
Anti-proliferative effects	Hepatocarcinoma	Study finding revealed that telomerase activity of HepG2 cells decreases after treatment with crocin	Salomi et al. (1991a)
Anti-proliferative effects of saffron extract and crocin	Malignant and non-malignant prostate cancer cell	The study concluded that both saffron extract and crocin can inhibit cell proliferation and arrest cell cycle progression	Aung et al. (2007a)
Cytotoxic and apoptosis induction	Prostate cancer	Finding based on result demonstrated a prostate cancer cell line to be highly sensitive to safranal-mediated growth inhibition and apoptotic cell death	Sun et al. (2013)
Chemopreventive effect of aqueous saffron	Skin carcinoma	Study result concluded that saffron inhibits skin carcinoma in mice when treated early	Wang et al. (1991)
Potential of saffron to induce cytotoxic and apoptotic effects	Lung cancer cells	Finding demonstrated that proliferation of the A549 cells was decreased after treatment with saffron	Sun et al. (2013)
Designed to elucidate apoptosis induction by crocin	Human pancreatic cancer	Crocin induced apoptosis and G1-phase cell cycle arrest	Zhang et al. (2013)

pathways and activation of apoptosis and retinoid-based signalling (Samarghandian et al. 2011). Saffron is an important chemopreventive agent owing to its bioactive molecules, crocin, crocetin, picrocrocin and safranal (Fig. 13.2) being the main anti-carcinogenic, antimutagenic, and immunomodulatory components (Bathaie et al. 2013a; Khavari et al. 2015).

Crocin delayed and reduced papilloma formation on a two-stage carcinogenesis (Konoshima et al. 1991; Li et al. 2015). Therefore, it can be used as a potential candidate for a safe drug against skin cancer. Crocetin has a chemical preventive function against oesophageal cancer by inhibiting cell proliferation, preventing the development of the cell cycle between the step S and G2, causing programmed cell death by increasing the production of bax proapoptotic protein and inhibiting the movement of carcinoma cells (Chryssanthi 2007). As an anticancer agent, crocetin induces its chemopreventive action via two distinct pathways – suppression of cell proliferation and activation of apoptosis. Inhibition of cell proliferation is dependent on concentration, and time-dependent on apoptosis induction (Alavizadeh and Hosseinzadeh 2014). Crocetin's showed dose-dependent inhibitory impact on cell proliferation (Mousavi et al. 2009) and caspase-dependent pathway through improved expression of Bax protein signifying its possible use as a chemopreventive agent for treating breast cancer (Samarghandian et al. 2014). Safranal is considered a potential therapeutic agent as it inhibits the proliferation of malignant cell line by apoptosis and inhibits cell growth by inducing apoptosis in the neuroblastoma cell line (Samarghandian et al. 2015). It can effectively protect the susceptible aged brain against oxidative damage by increasing the levels of GSH, SOD and GST supplemented by reducing lipid peroxidation (Bajbouj et al. 2012), enlightening that crocetin, crocin and safranal can be considered as a potential chemotherapeutic drug or as a cancer chemotherapy sensitizer.

Saffron causes DNA disruption and apoptosis in colorectal cancer cell lines and thereby reduces the chance of new cancer formation (Aung et al. 2007b). Saffron or its active constituents in culture may reduce the proliferation of some human cancer cells. Crocin considerably inhibited the growth and proliferation of colorectal cancer cells (D'Alessandro et al. 2013). The major constituent of saffron (crocin) tempted apoptosis in prostate cancer which repressed cell proliferation and arrested progression in the cell cycle (Dhar et al. 2009). A related proliferation limitation has been shown in culture of breast cancer cells. The proliferation of MDAMB231 and MCF-7 cells was significantly inhibited by constituents of saffron, transcrocin-4, crocetin and saffron extract (Mousavi et al. 2009). There was a significant regression of growth in in vivo pancreatic tumours due to apoptosis induced by crocetin treatment, and cell proliferation was inhibited (Hoshyar et al. 2013). Crocin might induce apoptosis in cancer cells where apoptosis depended on caspase activation by dose- and time-dependent regulation of adenocarcinoma (Bathaie et al. 2013b; Mousavi et al. 2014). In a cell cycle analysis utilizing flow cytometry, apoptosis activation in the gastric cancer tissue was demonstrated due to the administration of higher doses of aqueous saffron extract (Nair et al. 1995). Angiogenesis plays a crucial role in the growth and metastasis of tumours.

The various extracts of crocus are known to decrease vascular endothelial growth factor receptor expression by serving as an effective chemotherapeutic agent in breast cancer treatment (Mohajeri et al. 2009). Saffron extract has been reported to be useful as a preventive or therapeutic agent against diabetes mellitus with potential as a diabetes medication (Kang et al. 2012). The extracts are known to improve glucose synthesis and phosphorylation of AMPK (AMP-activated protein kinase) and MAPK (mitogen-activated protein kinases) in skeletal muscle cells and also enhance insulin sensitivity via insulin-dependent and insulin-independent pathways (Rajaei et al. 2013). In alloxan-induced diabetic rats, the hypoglycaemic and anti-hyperglycaemic essence of the ethanol saffron extract and its function in the regeneration of damaged pancreas have been demonstrated (Mousavi et al. 2010). Hypoglycaemic and antioxidant effects of crocin may be helpful in treating diabetes (Hosseinzadeh et al. 2005).

The aqueous extract of saffron (*Crocus sativus* L.) showed preventive function in the oxidative injury caused by renal ischaemia-reperfusion (IR) in rats (Fadai et al. 2014). The aqueous extract may avoid metabolic syndrome caused by olanzapine and insulin resistance and raise blood glucose in schizophrenia patients (Imenshahidi et al. 2013b). Aqueous extracts resulted in a dose-dependent reduction in mean systolic blood pressure (MSBP), with antihypertensive and normalizing effect (Xu et al. 2005). Crocin inhibits hyperglycaemic atherosclerosis by reducing cholesterol (stuff), low-density lipoproteins and triglycerides in the blood with decreased lipoprotein production (Higashino et al. 2014). Crocetin employs antihypertensive and antithrombotic special effects due to reduced nitric oxide inactivation by reactive oxygen species (Yan et al. 2010) resulting in increased bioavailability of nitric oxides. The cardioprotective role of crocin in cardiac toxicity triggered by isoproterenol is attributed to the regulation of oxidative stress, thus preserving the cell's redox state (Maes et al. 2011). Crocetin is therefore believed to improve oxygen consumption and longevity in the entire body. The inflammatory cascades were blocked in anaesthetized rats, and the development of reactive oxygen species was impaired in the heart after haemorrhagic shock (Akhondzadeh et al. 2005). Crocin protects the brain from excessive oxidative stress and is a potential therapeutic candidate for global transient cerebral ischaemia (Akhondzadeh et al. 2005). Development in the spatial processing skills after persistent cerebral hypoperfusion with crocin and saffron extract has been noted. A 30 mg regular dosage of saffron as a possible neuroprotective agent dramatically decreased the level of mild to severe depression on a standard assessment scale relative to placebo (Hosseinzadeh et al. 2012b). This may be attributed to saffron's antioxidant and radical scavenging effects in neurological conditions including depression and Alzheimer's disease (Farokhnia et al. 2014).

13.12 Other Possible Applications

The constituents of saffron have often been ascribed to be very distinct from the applications described above. Histological analysis showed that saffron improved re-epithelialization substantially in burn wounds. While the precise saffron function remains unknown, anti-inflammatory and antioxidant activity may have led to the greater healing of wounds. Another research was performed on the immune modulatory effect of saffron alcoholic extract and its impact on selective upregulation of Th_2 and it was proved that in all animal models used, *C sativus* greatly modulates the immune reactivity (Bani 2011). The therapeutic role of saffron for therapy includes its soothing and inhibitory effect on histamine (H1) and muscarinic receptors. Besides it is known to have relaxant effect on tracheal smooth muscle leading to bronchodilatory effect and may be used for asthma symptom relief (Bayrami and Boskabadi 2012).

In addition, saffron has been suggested for therapy for sexual disorders (especially due to major depression problems) in both males and females and erectile dysfunction in males. It has been from both animal and human experiments that saffron has beneficial aphrodisiac effects (Modabbernia 2012). Treatment with selective serotonin reuptake inhibitors (SSRIs) on humans showed beneficial effects on their sexual function by administering saffron extract simultaneously. In addition, saffron appeared to improve the sexual arousal, lubrication and pain domains of fluoxetine-related sexual dysfunction in women (Kashani 2013).

13.13 Conclusion

Saffron is a potential medicinal and prophylactic agent with action varying from anticancer to cognitive enhancer. The bioactive compounds contained in saffron, in particular crocetin and crocin, have been identified to be promising candidates for the treatment and control of different diseases. However, to get accurate results, comprehensive clinical trials must be conducted. Future studies are required in order to determine optimum dosage appropriate to the disease and to choose the best practicable mode of administration. Scientific studies will concentrate on looking for certain natural compounds that may function synergistically with saffron or its compounds to treat cancer-like malignancies.

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