Saffron (*Crocus sativus* L.): A Review

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Abstract

In this chapter, we have described about saffron with special emphasis to its pharmacological properties. We made an attempt to compile the literature available about saffron. Majority of you would have heard about this plant as a cosmetic ingredient but apart from that this is a commercial plant with several active principles. This chapter will throw some light on the biological, antioxidant and pharmacological properties of saffron. This chapter will help young researchers and students pursuing their early career and academics in the field of medicinal botany, pharmacology, ethnopharmacology and other allied fields. We made our sincere attempt to present this chapter with the latest information that is available on open sources.

Keywords

Saffron, Pharmacology, Alzheimer's, Cancer, Diabetes

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1. Introduction

Saffron is a perennial plant, originates from the genus *Crocus* (Family: Iridaceae). Worldwide, saffron includes 85–100 varities, widely distributed in the Mediterranean – Europe and Western Asia. The vital parts of saffron are dried (dark) red-orange stigmas (thread-like parts) of the flower. (Rezaee-Khorasany and Hosseinzadeh 2016).

Figure 1. Plant of *Crocus sativus* L.

(Source:http://www.plantsoftheworldonline.org/taxon/urn:lsid:ipni.org: names:436688-1)

Owing to its trading potential, this spice is popularly known as "Red Gold". It is the most expensive spice in the world. It has 24 chromosomes, however, the genome is yet to be explored completely (D'Agostino 2007). Being a geophyte, it is propagated by vegetative reproduction through the formation of daughter corms from the mother corm. In countries like Iran, Spain, Italy, Persia, Greece, Egypt, and India (Ayurveda), saffron is an economically and medically important product (Rezaee-Khorasany et al. 2019*)*. Since ancient times, it has been an expensive spice that served as a food coloring and flavoring agent (Javandoost et al. 2017). A study published by Moradi and Turhan (2017) revealed that more than 90% global production of saffron comes from Iran, whereas annually Herat region of Afghanistan produces 5–6 tons of saffron. In the current chapter, we made an attempt to collect and compile the information available on the online resources into a structured manuscript.

2. Vital Parts and Composition of Saffron

Let us explore in brief about the vital parts of the saffron and their composition in the coming subsection:

2.1. Stigmas

The stigmas of saffron contain the following contents in the respective percentages: 14-6% water, 11-13% nitrogenous substances, 12-15% sugars, 41-44% soluble extract, 0.6-0.9% essential oil, 4-5% fibers, and 4-6% ashes. It is interesting to know that nearly 160 volatile components of essential oil exist in stigmas (Carmona et al. 2007; Kanakis et al. 2004). Safranal is the major component found abundantly in saffron essential oil (60-70%) and comprises 2% of dry stigmas (Maggi et al. 2009; Masi et al. 2016). It is important to note that safranal is responsible for the aromatic nature of saffron (Buchecker and Eugster 1973).

2.2. Anthers

Anthers have high levels of proteins, sugars, and low levels of lipids (around 80.51% unsaturated), and to some extent microelements and antioxidant compounds.

2.3. Petals

Saffron petals are rich in crocin and kaempferol, providing significant source of bioactive compounds for the development of significant food products, pharmaceutical and cosmetic formulations.

Research studies conducted in the last decade have shown the capabilities of saffron byproducts (flower waste) such as spathes, leaves, corms and floral-derived juices as cheap sources for bioactive compounds (Termentzi and Kokkalou 2008; Argento et al. 2010; Serrano-Diaz et al. 2012, 2013; Sani et al. 2013; Zeka et al. 2015; Tuberoso et al. 2016; Lahmass et al. 2017, 2018; Menghini et al. 2018). So far, we have explored about the bio brief of saffron, now in the coming sections we will be knowing more about the bioactivities and pharmacology of saffron with special emphasis to its therapeutic as well as preventive potentials along with proven and published evidences available on online resources.

3. Biological Activities of Saffron

Saffron exhibits diverse therapeutic properties on various tissues and organs such as:

3.1. Antioxidant

It is well known that plants are rich sources of natural antioxidant molecules. However, saffron is rich in two carotenoids-crocin and crocetin. These two carotenoids play a significant role in overall health by acting as natural antioxidants. Crocin is the highly explored bioactive ingredient and is well known for its antioxidant properties. Crocin, in combination with components like safranal, dimethylcrocetin and flavonoids exhibits full potential of saffron (Hosseinzadeh et al. 2008). Studies conducted on human brain revealed that Saffron can control the deposition of amyloid β-peptide and is useful in preventing Alzheimer's disease (Bathaie et al. 2013). Apart from this there are published evidences showing the potential of saffron as an antioxidant, antimicrobial, anti-inflammatory and antidepression agent (Abbasvali et al. 2016; Hosseinzadeh and Younesi 2002; Moshiri et al. 2006; Li et al. 2004; Tirillini et al. 2006; Zeka et al. 2015; Ahrazem et al. 2018).

3.2. Anti-inflammatory and analgesic effect

Herbal remedies and edible supplements of natural origin are being used for preventing pain and inflammation (Tamaddonfard et al. 2019). Similar to this, extracts of saffron have been used to treat fever, healing wounds, and reducing lower back pain (Premkumar et al. 2003). Eghdami et al. (2013) study revealed that, aqueous and alcoholic extracts of saffron have an antinociceptive and anti-inflammatory activity for both acute and chronic pain.

3.3. Antispasmodic and digestive tonic

Literature review shows that safranal normalizes issues related to gastric ulcer and improves gastric protection. In addition to this, it is capable of restoring the histological changes induced by indomethacin (Hosseinzadeh and Nassiri-Asl 2013).

3.4. Anti-aging effect and skin related diseases

As discussed in the above sections, saffron is rich in antioxidants like crocin, quercetin and kaempferol. These molecules can be used to treat dermal related issues like erythema, characterized by inflammation, redness or rash. In folklore medicine, saffron along with olive and/or coconut oil and raw milk is applied on face as an effective way to exfoliate and improve blood circulation.

3.5. Anti-U.V. agent

Prolonged direct exposure to UV rays (strong sun light) is extremely harmful and may cause serious lesions. Products of saffron known to have ability to protect skin from harmful UV rays. Hence, saffron and its products are used as natural protecting agents (Tabrizi et al. 2003; Golmohammadzadeh et al. 2010).

3.6. Redness or dark spots

The terpenoids of saffron especially monoterpenoids like, crocin, quercetin, kaempferol, and other phenolic components are known to reduce melanin. Owing to this reason, saffron acts as very effective whitening agent for the skin. Tyrosinase enzyme catalyzes the melanogenesis which is accomplished by a series of oxidative reactions (Ferrence and Bendersky 2004). Terpenoids of saffron acts by inhibiting the activity of tyrosinase (De Leeuw et al. 2001).

3.7. Anti-atherosclerotic activity

Atherosclerosis is a pathological condition that includes heart and its associated arteries. In this pathogenesis is caused due to the adhesion and migration of various types of leukocytes on endothelium. Cytokines and other signaling molecules play a crucial role in the progression of atherosclerotic plaque and its advancement. Some of the mechanisms through which saffron protects the heart from the development of atherosclerosis are:

i. Saffron acts through hypercholesteremic mechanisms, improving the clinical course of atherosclerosis and cardiac ischemia (Gainer et al. 1993; Huang et al. 2016; Imenshahidi et al. 2010). Saffron also increases the phosphorylation of Akt/GSK-3b/eNOS proteins, through this it reduces the expression of IKK-b/NF-KB (Bharti et al. 2012; Fatehi Hassanabad et al. 2004; Hosseinzadeh and Sadeghnia 2005; Rezaee and Hosseinzadeh 2013).

ii. Crocetin suppresses Advanced Glycation End products (AGEs) leading to leukocyte migration and consequent suppression of intercellular adhesion molecule 1 expression (Xiang et al. 2006; Alavizadeh and Hosseinzadeh 2014; Xu et al. 2007).

iii. Another way of protecting the progression of atherosclerosis is by decreasing the uptake of oxidized LDL by macrophages that indirectly reduces the formation of foam cells and atherosclerotic plaque (He et al. 2005).

iv. Inhibition of pancreatic lipase is one of the mechanisms through which crocin acts as hypolipidemic, thus limiting the absorption of fats and cholesterol (Kamalipour and Akhondzadeh 2011). This indirectly minimizes the intake of high calorific diet (Melnyk et al. 2010). At the outset, crocin regulates the body weight and fat deposition (Mashmoul et al. 2013).

3.8. Diabetes mellitus

Hyperglycemia and generation of reactive oxygen species are the most common risk factors associated with diabetes mellitus. Studies conducted on saffron extracts proved increased glucose uptake and insulin sensitivity in muscle cells (Assimopoulou et al. 2005; Shirali et al. 2013; Kang et al. 2012). Bioactive principles of saffron shown to increase the secretions of pancreatic beta-cells, that regulates the glucose metabolism and control dyslipidemia (Eghdami et al. 2013; Altinoz et al. 2015; Kianbakht and Hajiaghaee 2011; Naghizadeh et al. 2014).

3.9. Effects on vision (eyes)

The "kohl" pencils, a combination product of cloves, rosewood, saffron and antimony was used by Egyptians in ancient times to blacken the eyes. It is observed that saffron extracts can reduce cataracts (Makri et al. 2013), retinal degeneration (Serrano-Díaz et al. 2012), corneal disease, sore eyes (McGee 2004; Khorasani et al. 2008), regulates blood circulation leading to improved retinal function, and in the treatment of eye infections (Xuan et al. 1999; Makri et al. 2013).

3.10. Antidepressant

Globally, depression is one of the most common diseases. It affects about 11.6% of the world's population (Suganya et al. 2016). Both safranal and crocins found in saffron, modulates the uptake of neurotransmitters like dopamine, serotonin (5 HT), and norepinephrine and human monoamine oxidase A and B (Hill 2004; Hosseinzadeh et al. 2004; Khazdai et al. 2015) and increases affinity towards cyclic AMP (Adenosine monophosphate) (Ghasemi et al. 2015; Razavi et al. 2017; Vahdati et al. 2014). It is evident by clinical studies that hydroalcoholic extract of saffron at the dose of 20-30 mg/day has improved mild to moderate depression (Akhondzadeh et al. 2004, 2005; Akhondzadeh et al. 2007; Noorbala et al. 2005, Kell et al. 2017, Kashani et al. 2018).

3.11. Alzheimer's and Parkinson's diseases

Both these disease states are attributed to the old age and loss of memory. Alzheimer's is a neural disorder that mainly affects brain and impacts the abilities like memory and thinking. Alzheimer's is characterized by an elevated deposition of β-amyloid peptide (Aβ) plaques in the brain. Extracts of saffron especially prepared from stigma and crocins have been tested as adjuvant treatment in Alzheimer's and Parkinson's diseases (Ahmad et al. 2005; Akhondzadeh et al. 2010b, 2010a; Pitsikas 2015; Nam et al. 2010; Geromichalos et al. 2012; Finley and Gao 2017; Tsolaki et al. 2016, Farokhnia et al. 2014).

In case of Parkinson, the safranal extract and compound crocetin showed preventive action against age related macular degeneration (regulating Keap1/Nrf2 signaling pathway) (Pan et al. 2016; Mohammadzadeh et al. 2018; Bisti et al. 2014).

3.12. Anticarcinogenic

Bioactive principles of saffron in combination with pharmaceutical salts like sodium selenite or sodium arsenite studied extensively to treat cancer. These two molecules are of great interest for scientists across the globe to study cancer prevention using *in vitro* and *in vivo* models (Hamidreza et al. 2010; Akhondzadeh et al. 2010; Abdullaev 2006).

i. Studies conducted on tumor cells revealed that inducing apoptosis could be one of the approaches of saffron extracts in preventing cancer (Escribano et al. 2000; García Olmo et al. 1999; Geromichalos et al. 2014; Bakshi et al. 2010; Bathaie et al. 2013; Nair et al. 1991, 1995; Smith 1998; Riverón 2002).

ii. Experimental studies shown that crocetin inhibits gastric tumors in a dose dependent manner (Bathaie et al. 2013).

iii. Carotenoids extracted from saffron, exhibit inhibitory effect on free radicals and reactive oxygen species (Abduallev and Frenkel 1999; Molnár et al. 2000).

3.13. Sexual dysfunction

Globally, spices are recognized for their aphrodisiac ability. Moreover, saffron is a popular traditional ingredient in many ancient and modern cultures across the globe.

i. It is evident that saffron plays a significant role in controlling sexual disorders due to the presence of fluoxetine and other selective serotonin reuptake inhibitors (SSRI) (Modabbernia et al. 2012). It also enhanced the erection duration especially in patients suffering from erectile dysfunction (Kashani et al. 2013).

ii. Active principles of saffron could inhibit extra and intra cellular Ca^{2+} release from endoplasmic reticulum (He et al. 2004), which later contributes to erection (Williams et al. 2005; Safarinejad et al. 2010; Shamsa et al. 2009).

3.14. Cosmetology and perfumery uses of saffron

Crocin and kaempferol, present in saffron acts as potential sources for cosmetic formulations (Ahrazem et al. 2018; Zeka et al. 2015; Li et al. 2004).

3.15. Saffron as natural pigment in cosmetics

In folklore recipes, plant pigments like chlorophyll, curcumin (turmeric), and carotenoids are popular food coloring agents and also used in cosmetics. In ancient Indian (Ayurveda), Mongolian, Chinese, Egyptian, Greek and Arabian literature, saffron has been considered as a panacea (cure-all). Saffron is used as an alternative for turmeric in light sensitive conditions (Colledge 2005).

3.16. Perfumery

In the ancient Greece (around 2000 to 146 BC) royal traditions, saffron was used as a perfume in salons, courts, theaters and bathrooms. Afterward, it became a house hold spice (Abrishami1987; Giaccio 2004).

3.17. Healing of second-degree burns

Saffron has shown a significant effect on wound healing by encouraging the re-epithelialization of burn wounds (Mashmoul et al. 2014).

4. Pharmacology

The three important pharmacological ingredients of saffron include crocin, picrocrocin, and safranal (Figure 2). Also, it is composed of a complex mixture of volatile and non-volatile compounds. The bright red, golden-orange color of saffron is due to the presence of water-soluble carotenoid, notably crocin ($C_{44}H_{64}O_{24}$). It is derived from the oxidative cleavage of the carotenoid zeaxanthine. Picrocrocin ($C_{16}H_{26}O_7$, 4-β-hydroxy cyclocitral glucoside), another major constituent of saffron is responsible for its bitter taste (Alonso et al. 2001; Masi et al. 2016). Safranal, a monocyclic terpene aldehyde (2,6,6 trimethyl 1,3-cyclohexadiene-1-carboxaldehyde) is derived from hydrolysis of picrocrocin ($C_{10}H_{14O}$) and produces aroma (Hosseini et al. 2018). It is interesting to know that, safranal is not present in fresh plant, but during the drying phase, it is produced as by-product of oxidation.

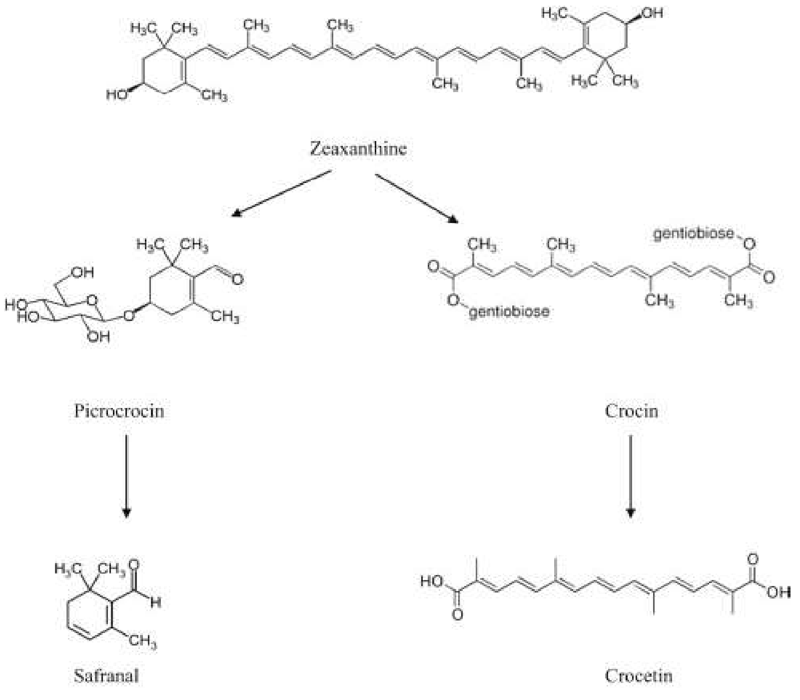

Figure 2: The biological active compounds of saffron

(Source: https://www.sciencedirect.com/science/article/pii/B9780128184622000139)

5. Conclusion

Our chapter concludes that saffron with wide range of usefullness as medicinal and commercial plant may represent an efficacious and potent candidate in the process of discovering plant based drugs for various diseases.

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