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SAFFRON: A Mini Review on its Medicinal Potential

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ABSTRACT: Saffron is a stigma of a plant that is dried and then used as a Spice in Food and Beverages and mostly cultivated at the Higher Altitudes. It is well known for the cure of diseases like Diabetes, Hypertension, Depression, Cancer, and Obesity. Researchers have stated that it's also beneficial to treat respiratory disorders also. It is one of the most important spices in Ayurveda Sciences and its aromatic nature & flavour makes it more valuable for all the Food Industries. There are many carotenoid compounds present in saffron, although widely reported and studied are crocin and crocetin. Despite the fact that saffron has such a great deal of therapeutic potential, still there is a gap in the pharmaceutical outcome under its name and in this review, we have highlighted the advantages, furthermore briefly examined the medicinal and therapeutic application of saffron.

Keywords: Saffron, Phytochemistry, Crocetin, Cancer, Crocin, Medicinal

INTRODUCTION

Saffron is one of the world's most expensive spices. Its scientific name is termed *Crocus sativus* which belongs to the Iridaceae family (Cardone *et al.,* 2020). It is the dried stigma of the flower of crocus sativa which mainly occurs in the Red color. It is mainly cultivated in the High-Altitude Areas and the soil is well-drained & highly rich in organic matter. It is considered as both the aromatic element and a colorant, extracted from Mother Nature. It is widely used in the preparation of medicinal products and Dye, also mostly used as a flavoring agent in Food and Beverages. It was first originated and cultivated in Greece and currently, it is widely produced by the countries like Iran, Morocco, and India.

This natural product is around 400 years old and people called it "Red Gold" (Leone *et al.,* 2018). It was first originated and cultivated in Greece and currently, it is widely produced by the countries like Iran, Morocco, and India. As per the increasing cases of chronic diseases like Cancer, food industries are now focusing on spices and preservatives. The addition of spices, which are rich in nutritional properties and preservatives in the food products, are helping in the maintenance and treatment of Human Health. Thus, the saffron is most demanding spice among the food industries and Consumers (Kyriakoudi *et al.,* 2015). In the early times, saffron was also used as a dyeing agent to color the robes of the Buddhist monks. It also has Ayurvedic properties which cure the diseases like Arthritis and Respiratory disorders like Asthma and Cough.

To enhance the profit from the cost of saffron, Researchers started focusing on the development of its Leaves, stamens, petals, and other parts (Lahmass *et al.,* 2018; Chichiriccò *et al.,* 2019). The by-products of saffron can be buried under the soil as an organic fertilizer and also provide nutritional value like the food supplements, which makes it more valuable in the terms of Economic factors.

A. Phytochemistry of Saffron

Crocus sativus is a very useful plant crop with medicinal benefits and is a common spice plant because of its strong odour and bright yellow colour. Photochemical researches have revealed that the colour is mainly due to the degraded carotenoid compounds, crocin and crocetin and the flavour of Crocus sativus comes from the carotenoid oxidation products, mainly safranal and the bitterness comes from glycoside picrocrocin (Pander and Schurtenberger 1982) suggested a proposal for biogenesis of the colour and odour active compounds which may be derived by bio-oxidative cleavage of zeaxanthin. The major principle of *C. natives* is safranal, which is a carboxaldehyde volatile chemical compound that can simply be formed by de-glycosylation of picrocrocin. (Gohari *et al.,* 2013)

B. Medical Scenario of Saffron

Sativus (Saffron) has been used extensively as a food colour and is a rich and relish flavouring and seasoning ingredient. Traditionally saffron was used colossally in Ayurvedic medical science as a sedative, expectorant to treat coughs, anti-asthmatic agent, emmenagogue for women's reproductive health (Gohari *et al.,* 2013) Many Researchers have done various remarkable discoveries and developments using *C. sativus* in the field of medicine. These researchers have described various potential uses of C. *sativus* as a natural cure to many diseases. Saffron has given a positive response in curing and controlling various diseases and disorders which were difficult to manage.

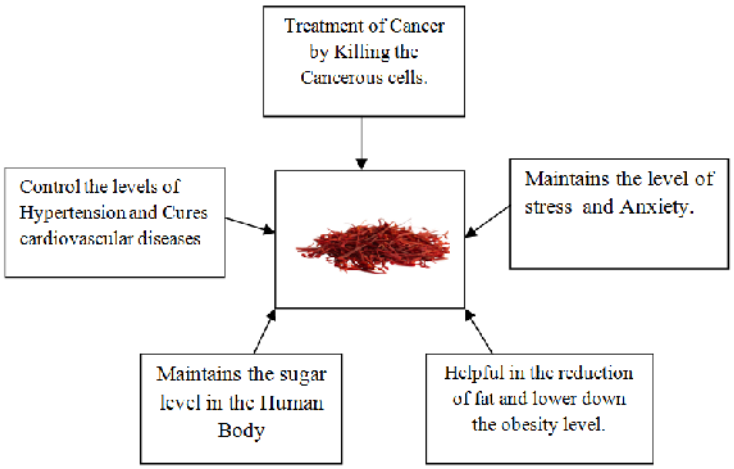

Fig. 1. The above diagram represents the pharmacological features of Saffron and Various medicinal benefits of saffron.

Diabetes Mellitus. Diabetes is one of the chronic medical condition which has a great threat on the human lives (Zou *et al.,* 2018). The characteristic symptom of Diabetes is the rise in the blood sugar levels as compared to the normal levels caused due to irregular insulin secretions or their resultant biological responses (Lonappan *et al.,* 2007). Diabetes can pose many complications which are the prime reason for various morbidities and mortalities like, atherosclerosis, which is the conscription of monocytes and lymphocytes, further triggering the accumulation of the oxidized LDL at the artery walls (Lusis, 2010), nephropathy, which is the dysfunction of the kidney, retinopathy (Razavi & Hosseinzadeh, 2017).

Various studies have been reported on the antidiabetic and hypoglycaemic effects of Crocus sativus and its derived bioactive compounds. In a study, a dose of hydro methanolic extract of *C. sativus* of 50 mg/kg concentration to the healthy male rats which after 1 week of dosing showed a drastic decrease in serum glucose, and after 2 weeks of treatment serum insulin levels increased towards normal levels.

Another study was carried out in STZ-induced diabetic rats in which the rats were given a dose of Crocin of concentration about 50 and 100 mg/kg. The results showed a significant drop in the serum glucose levels and new, advanced end-products of glycation were produced.

One study conducted on the C2C12 skeletal muscle cells showed that saffron can increase uptake of glucose and also can make phosphorylation of AMP-activated protein kinase and acetyl-CoA carboxylase more efficient. (Razavi & Hosseinzadeh, 2017).

All these studies suggested that saffron and its active components can be used as a potential therapeutic agent for the controlling of Diabetes Mellitus by various pathways and mechanisms related to increased insulin levels, dropping down glucose levels.

Hypertension. Hypertension is one of the most common metabolic disorders and the major cause of cardiovascular diseases like Coronary artery disease (CAD), cardiac arrest, heart failure, and many more. Various drugs for controlling hypertension are available in the market but many of them can cause adverse reactions. Saffron and its bioactive components can control hypertension and protect against cardiovascular destruction (Razavi & Hosseinzadeh, 2017).

One study showed that the aqueous extract of saffron has two bioactive components crocin and safranal which were able to reduce the levels of mean arterial blood pressure in the hypertensive rats when the appropriate dose was administered. Also, it showed that safranal is more important in the reduction of blood pressure (Abe and Saito, 2000).

Mohebbati *et al.* carried out a study that showed that petals of the saffron flower have an effect on the angiotensin II AND nitro-L-arginine methyl ester-induced hypertension by increasing systolic blood pressure and mean arterial pressure. Therefore, saffron petals pre-treatment can control hypertension (Mohebbati *et al.,* 2020).

Depression and Anxiety. Depression and anxiety are the two most commonly existing mental disorders. Various treatments and medications are available for the betterment of depression and anxiety patients like; psychotherapy, various antidepressant medications, electro conclusive therapy (Shafiee *et al.,* 2018).

Several studies have compared the effects of saffron and commonly available antidepressant drugs. It showed that saffron (30mg/day) has similar effects on patients with mild to moderate depression as antidepressant drugs like fluoxetine, imipramine, and citalopram (Shafiee *et al.,* 2018). Also, a trial was conducted by Mazidi et al. in which 50 mg saffron capsule was given to 60 patients for 12 weeks and it was observed that the depression and anxiety symptoms reduced to a great extent. (Mazidi *et al.,* 2016)

All these studies evidence that saffron can be used as a potential agent for the treatment of mild to moderate depression and anxiety symptoms.

Cancer. Cancer is one of the important and frequent causes of death in the world. An important impact on

tumour development risk is represented by the adopted lifestyle. Several solid tumours are treated with surgery, radiotherapy, and chemotherapy, alone or in combination, and, in the last years, many different chemotherapy agents were discovered and some of these were also introduced in current therapy. Anyway, the majority of chemotherapeutic agents have serious side effects. Nowadays, natural products or plant derivatives are used as chemoprevention drugs and chemotherapy is the new approach that uses specific cell premalignant transformation in the malignant form.

Saffron and its carotenoids have been shown to have anti-oxidant function, cancer cell apoptosis, inhibition of cell proliferation, enhancement of cell differentiation, control of cell cycle progression and cell growth, modulation of tumour metabolism, stimulation of cell-to-cell interaction, and immune modulation. According to the studies reviewed in this study, the anticancer role and possible therapeutic effects of saffron and its compounds are mainly attributed to carotenoids' antioxidant properties. The exact mechanism of anticancer activity of these compounds is unknown. These findings have not yet been verified. Crocin's bioavailability must be improved through the advancement of various Drug Delivery Systems (DDS) that can avoid intestine degradation and increase pharmacological active blood concentrations while also allowing for different loco regimes.

The effects of the phytochemicals have been widely documented to act directly or indirectly on the target through multiple signalling pathways and networks in cancer cells (Lee *et al.,* 2003). Age appears to be the most important risk factor for cancer, and several hypotheses have been established in this regard (Smetana *et al.,* 2016). The "oxidative stress theory" is the most well-known and, at the same time, most important theory among them. Here, the main role is played by the endocrine system that may induce age-related endocrine disorders and sustain cancer progression (Vitale *et al.,* 2013). Deregulated development of Reactive Oxygen Species (ROS), such as superoxide anion radicals, hydrogen peroxide, hydroxyl radicals, and peroxyl radicals, is also well known to play a role in the carcinogenesis process (Yang *et al.,* 2016). Recent research has shown even more evidence of the dynamic interplay between aging and cancer mechanisms. In non-cancerous fibroblasts in the tumour microenvironment, increased intra-tumour ROS levels can cause aerobic glycolysis and autophagic degradation (Costa *et al.,* 2014). The cellular antioxidant system, composed of different enzymes responsible for the elimination and neutralization of ROS, balances ROS generation with ROS degradation. An increased oxidative stress status represents an important feature in cancer promotion (Pereira *et al.,* 2016). Saffron extract has a huge number of carotenoids that can interact with antioxidant enzymes promoting their ROS degrading function and crocin proved the most active antioxidant element of saffron (Bolhassani *et al.,* 2014, Bathaie *et al.,* 2014, Milani *et al.,* 2017). A series of epidemiological studies resulted in a close correlation between a high dietary saffron carotenoid intake and a reduced risk of cancer.

Crocetin was applied topically to 12-Otetradecanoyl phorbol 13-acetate (TPA)-induced skin tumours that had been pre-treated with benzopyrene (BP), which decreased the number of tumours (Wang *et al.,* 1995). Furthermore, crocetin can inhibit the TPA-induced expression of hydrogen peroxide and myeloperoxidase when applied locally to the skin of animals at various concentrations. Crocetin's inhibitory role in tumour cells is due to its reducing power and ability to interfere with DNA, RNA, and protein synthesis, as well as inhibiting Protein Kinase C function (Giaccio, 2004).

Crocin chemosensitizes A278 ovarian cancer cells to cisplatin, according to a recent report, which is mediated by a reduction in MRP1 and MRP2 resistance-related protein expression. Crocin inhibited cell growth on HO-8910 by upregulating the apoptosis-related proteins p53, FAS/APO-1, and Caspase-3, which resulted in an increased cell percentage in GO/G1 and apoptotic death (Mahdizadeh *et al.,* 2016, Xia *et al.,* 2015).

Crocin caused increased DNA fragmentation in MOLT-4 human Leukemia cancer cells, which were treated with the drug at concentrations ranging from 50 to 500 M (Rezaee *et al.,* 2013). After treatment with crocin, Jurkat Leukemia cells showed the same mechanism of apoptosis induction as other Leukemia cancer cells, marked by a decrease in Bcl-2 and an increase in BAX protein expression (Sun *et al.,* 2016).

In vivo studies also revealed that when animals were given crocin, the growth of N-Nitroso-N-Methyl-Urea-induced breast cancers was slowed. The authors demonstrate that p53 is needed for induction of apoptosis, inhibition of cell cycle progression, and downregulation of cyclin D1 and p21Cip1 expression in these experiments (Ashrafi *et al.,* 2015).

Crocetin has recently been shown to have anti-inflammatory properties in vivo and in vitro, reducing the role of IL-1beta, TNF-alpha, and PMNs in Methylcholanthrene-induced cervical cancer cells. The reduction of COX-2 development was dose-dependent in the same cancer model, bolstering the evidence of crocetin's anti-inflammatory effects and bolstering the concept of crocetin as a chemo-preventive and anti-inflammatory drug (Chen, 2015). Crocin is a liposomal encapsulated form increases HeLa cell apoptosis and crocin's antitumoral properties in vivo (Mousavi *et al.,* 2011).

Therefore, saffron has various anticarcinogenic properties which make it a useful therapeutic agent for the betterment of cancer patients.

Obesity. Obesity is a very common nutritional disorder in which there is an accumulation of excess body fat in the body due to excess calorie intake than calories burnt. Obesity is the underlying cause of various diseases like hypertension, liver cirrhosis, heart disease, cancer, and many more. Various anti-obesity drugs are approved but they have poor safety and efficacy.

A study showed that the dosage of crocin about 80 mg/kg concentration results in a decrease of body weight gain rate and also overall BMI of the body. Another study was carried out in obese rats in which saffron hydromethanolic extract was compared against placebo. The resulting observation showed that saffron and its active constituents were successfully able to reduce the overall body weight, leptin levels were normalized and food intake was also reduced (Razavi & Hosseinzadeh, 2017).

In the recent study by Ramli *et al.* in which saffron and crocin were added to the high-fat diets of the obese rats and given for 8 weeks. The study revealed that saffron was able to improve the metabolic profile of the rats by managing the down regulation of various metabolites like alanine, lactate, and creatinine (Ramli *et al.*, 2020).

All the studies confirm that saffron has anti-obese properties which can be potent enough to control obesity by acting on various pathways like reduction in body weight, reduction in food intake, down regulation of metabolites, and many other factors to improve the metabolic profile.

CONCLUSION

Saffron is a powerful spice high in antioxidants. It has been linked to health benefits, such as improved mood, libido, and sexual function, as well as reduced PMS symptoms and enhanced weight loss, additionally saffron is mainly grown in areas located at higher altitudes. The dried stigma of *Crocus sativa* is used as a flavouring and colouring agent and is also used in the preparation of medicines that cure the diseases like Diabetes, Depression, Hypertension, and Cancer. Also, it has been reviewed that obesity can be treated by Saffron. The Carotenoid compound present in it plays a major role in Medical Sciences and helps in increase in metabolic rate of the body.

That being said, the exact mechanism of these compound's anticancer actions is unclear. Furthermore, these results have yet to be confirmed in human clinical trials, and more research is required to determine the effectiveness of saffron in cancer diagnosis and treatment. The promising pharmacological properties of saffron carotenoids may be fully recognized following further research for commercial production as nutraceutical and pharmaceutical products to be used in any disease, as suggested by numerous data collected in this study. Despite the fact that the average dietary intake of saffron-derived carotenoids is still too poor to yield a meaningful result, saffron derivatives can still be used in the treatment of various diseases including cancers. As a result, it is important to improve crocin bioavailability by developing advanced delivery systems that can inhibit intestine loss, maximize pharmacological active blood levels which could enable it for different locoregional administrations.

However, in order to establish useful clinical trials, more research is required to better understand the true potentiality of compounds on humans.

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