

Review

The effect of saffron (*Crocus sativus* L.) and its ingredients on the management of diabetes mellitus and dislipidemia

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The rapidly increasing incidence of diabetes mellitus is becoming a serious threat to mankind's health in all parts of the world and is in a group of metabolic disorders having hyperglycemia as a common manifestation. Implication of oxidative stress in the pathogenesis of diabetes is proposed, not only by oxygen free-radical generation, but also due to non-enzymatic protein glycosylation, auto-oxidation of glucose, impaired glutathione metabolism, alteration in antioxidant enzymes, and lipid peroxides formation. Moreover, oxidative stress induces systemic inflammation, endothelial dysfunction, impaired secretion of pancreatic β cells and impaired glucose utilization in peripheral tissues. Nowadays, the use of antioxidants still remains a controversy, but its use as a therapy for diabetes can be considered, because it demonstrated effectiveness in lowering the risk of diabetes and its complications. Therefore, this review provides an updated overview of experimental *in vitro* and *in vivo* investigations on the biological activities of saffron (*Crocus sativus* L.) and its principal phenolic ingredients, especially focusing on their anti-diabetics effect. This data has led to the suggestion that saffron (*C. sativus* L.) and its principal phenolic ingredients might be beneficial for preserving diabetes and its complications; however, the application remains controversial. Therefore, this review highlights the antidiabetic effects of saffron and its main ingredients, related to antioxidant properties of carotenoids of saffron.

Key words: Antidiabetic, antioxidant, dyslipidemia, saffron.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by relative or absolute deficiency of insulin secretion and/or insulin resistance that causes chronic hyperglycemia and impaired carbohydrates, lipids, and proteins metabolism (Chaturvedi et al., 2007). DM is the principal factor responsible for high prevalence of mortality

due to coronary heart disease. Increased oxidative stress is a widely accepted participant in the development and progression of diabetes and its complications, while on the other hand, hyperglycemia engenders free radicals, and it also impairs the endogenous antioxidant defense system in many ways during diabetes (Boynes et al., 1991;

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Maritim et al., 2003). Diabetes-linked alterations in antioxidant defense system enzymes, such as catalase, glutathione peroxidase and superoxide dismutase have been demonstrated (Robertson et al., 2007), while insulin and oral anti-hyperglycemic drugs are the cornerstone of the diabetes treatment; they have important adverse effects and cannot always prevent diabetes complications significantly (Dey et al., 2002; Gilbert et al., 2009). Thus there is a continuing need for alternative anti-diabetic remedies with better risk-benefit ratios and greater patient acceptability. Herbal medicines derived from plant extracts are being increasingly utilized to treat a wide variety of clinical disease. More attention has been paid to the protective effects of natural antioxidants against chemically induced toxicities (Neelesh et al., 2010; Samini et al., 2013). Antioxidant therapy may play great role for diabetic patients; therefore, it can be considered for treatment of oxidative stress in DM and may be good choices for diabetes therapy. Phenolic compounds (e.g., phenolic acids, flavonoids, quinones, and tannins) are natural antioxidants abundant in many desert and steppic plants (Schroeter et al., 2002; Samarghandian et al., 2012). A positive linear correlation was indicated between the antioxidant activity and the total phenolic content in plants (Al-Mustafa et al., 2008; Tawaha et al., 2007), proposing that phenolic compounds contribute significantly to the antioxidant capacity of the plant. Direct correlation between the antioxidant property of medicinal plants and the latter's anti-diabetic activity was found (Sabu et al., 2002), and the relationship between the molecular structure of flavonoids and their radical-scavenging capability was found. However, there are many controversies nowadays on the role of antioxidant therapy for diabetic patients (Rahimi et al., 2005). Thus, this review provides an updated overview of experimental *in vitro* and *in vivo* investigations on the biological activities of saffron (*Crocus sativus* L.) and its principal phenolic ingredients, especially focusing on their anti-diabetics effect. Potential use of these natural agents for controlling diabetes complications is also discussed.

TRADITIONAL APPLICATION OF SAFFRON

Saffron is the dried stigmas of *C. sativus* L. *C. sativus* L belongs to the family of Iridaceae, the line of liliaceae, and is mainly cultivated in several countries of mild and dry climate (Abdullaev et al., 1993). Although, the source of saffron is unknown, it apparently originated in the area of Iran, Turkey and Greece, but now it is also successfully cultivated in European countries as Spain, Italy, France, and Switzerland, as well as in Morocco, Egypt, Israel, Azerbaijan, Pakistan, India, New Zealand, Australia and Japan. While the world's total annual saffron production is estimated to be 190 tons, Iran produces about 90% of the total with a commercial cost

(Abdullaev et al., 2007; Zarinkamar et al., 2011). The main reason for its great cost is that saffron is still cultivated and harvested as it has been for millennia by hand (Hosseinpour et al., 2010). Saffron's name is derived from the Arab word for yellow, a name reflecting the high concentration of carotenoid pigments present in the saffron flowers' stigmas which contribute most to the color profile of this spice. From ancient times, the saffron is widely used as drug to promote health and fight disease and it is also valued as a food additive for tasting, flavoring and coloring, as well as for its therapeutic properties (Abdullaev et al., 2007). In the traditional medicine, saffron is used as a diaphoretic, eupeptic, tranquilizer, expectorant, aphrodisiac, abortifacient, emmenagogue and in the treatment of hepatic disorders, flatulence, spasm, vomiting, dental and gingival pain, insomnia, depression, seizures, cognitive disorders, lumbago, asthma, cough, bronchitis, colds, fever, cardiovascular disorders and cancer. Saffron is recognized as an adaptogen in Indian ayurvedic medicine (Kianbakht et al., 2009).

CHEMISTRY OF SAFFRON AND ITS INGREDIENTS

Saffron contains more than 150 volatile, non-volatile and aroma-yielding compounds which consist of lipophilic and hydrophilic carbohydrates, proteins, amino acids, minerals, mucilage, vitamins (especially riboflavin and thiamine) and pigments including crocin, anthocyanin, carotene, lycopene, zizantol, flavonoids, starch, gums, and other chemical compounds. Based on chemical analyses of dry stigma of saffron extracts, carotenoids, namely crocin and crocetin and the monoterpene aldehydes picrocrocin and safranal are the most important active carotenoid secondary metabolites of saffron. Crocin, with elementary composition $C_{44}H_{64}O_{24}$ and molecular weight 976.96, is a hydrophilic carotenoid (8'-diapocarotene-8,8'-dioic acid), constitutes approximately 6 to 16% of saffron's total dry matter depending upon the variety, growing conditions, and processing methods (Gregory et al., 2005). This is the diester formed from the disaccharide gentiobiose and the dicarboxylic acid crocetin. Deep red color of crocin produces the color of saffron. Crocin 1 (or α -crocin), a digentiobioside, is the most abundant crocin with a high solubility being attributed to these sugar moieties. Crocin widely used as a natural food colorant (Lage et al., 2009). In addition to crocin, saffron contains crocetin as a free agent and small amounts of the pigment anthocyanin, α -carotene, β -carotene, and zexanthin (Lage et al., 2009). The structure of crocetin is presented as shown in Figure 1. Crocetin, with elementary composition ($C_{20}H_{24}O_4$), melting point 285°C and molecular weight 328.4, is an amphiphilic low molecular natural carotenoid (8, 8'-diapo-8, 8'-carotenoic acid) and consists of a C-20 carbon chain with seven double

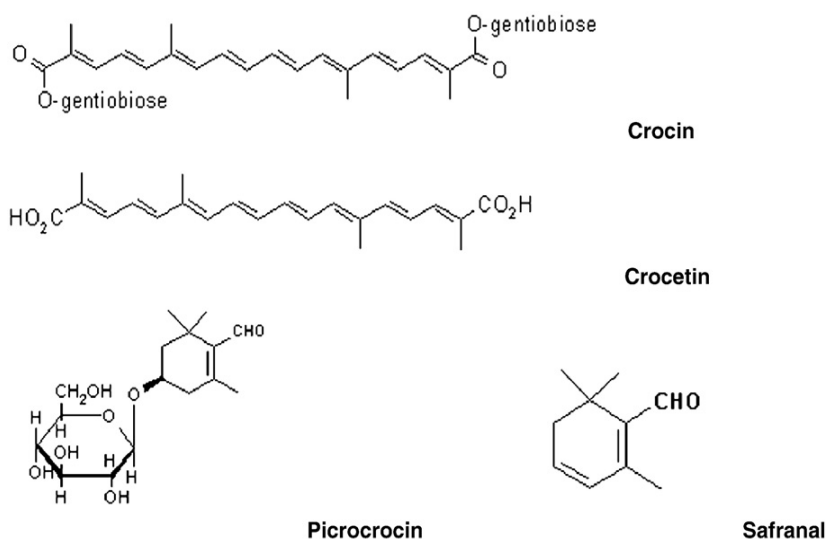


Figure 1. Chemical structures of crocin, crocetin, picrocrocin, and safranal.

bonds and a carboxylic acid group at each end of the molecule. This compound present in the central core of crocin and responsible for the color of saffron, constitutes approximately 14% of saffron's total dry matter depending upon the variety, growing conditions, and processing methods. It is a soluble in organic bases and slightly soluble in aqueous solution (20 μM at pH 8.0) (Lage et al., 2009). The structure of crocetin is as shown in Figure 1. Picrocrocin, with elementary composition ($\text{C}_{16}\text{H}_{26}\text{O}_7$) and molecular weight 330.37 g/mol is the main bitter crystalline terpene-glucoside of saffron. The actual taste of saffron is derived primarily from picrocrocin which is the second most abundant component (by weight), accounting for approximately 1% to 13% of saffron's dry matter (Alonso et al., 2001). Action of β -glucosidase on picrocrocin liberates the aglycone 4-hydroxy-2, 6, 6-trimethyl-1-cyclohexene-1-carboxaldehyde (HTCC, $\text{C}_{10}\text{H}_{16}\text{O}_2$), which is transformed to safranal by dehydration during the drying process of the plant material. Natural de-glycosylation of picrocrocin will yield another important aroma factor, safranal, ($\text{C}_{10}\text{H}_{14}\text{O}$) which comprises about 60% of the volatile components of saffron. Dehydration is not only important to the preservation of saffron, but is actually critical in the release of safranal from picrocrocin via enzymatic activity, the reaction yielding D-glucose and safranal, the latter being the volatile oil in saffron. Safranal, with elementary composition ($\text{C}_{10}\text{H}_{14}\text{O}$) and molecular weight 150. 21 g/mol is the major volatile oil responsible for the aroma (Lage et al., 2009). The stability of saffron and its ingredients is also dependent upon temperature, light and humidity on degradation of potency under storage conditions. Ingredients of saffron can be stored under -20°C and pharmacological activities as a supplement

remain unaltered for at least 2 years or even longer (Hosseinpour et al., 2009).

Toxicological studies have identified that the toxicity of saffron has been found to be quite low and oral LD_{50} of saffron in animal was 20.7 g/kg administered as a decoction. It has been demonstrated that oral administration of saffron extract at doses from 0.1 to 5 g/kg was non-toxic in mice. Ames/Salmonella test system revealed that crocin and dimethyl-crocetin isolated from saffron were non-mutagenic and non-toxic (Nair et al., 1995). Saffron should always be obtained from a reputable source that observes stringent quality control procedures and industry-accepted good manufacturing practices. People with chronic medical conditions should consult with their physician before taking the herb. Pregnant women should never take the herb for medicinal purposes, as saffron can stimulate uterine contractions (Abdullaev and Espinosa-Aguirre, 2004).

BIOMEDICAL FINDING OF SAFFRON AND ITS INGREDIENTS

Biomedical findings have been demonstrated that saffron and its ingredients may be useful as a treatment for neurodegenerative disorders and related memory impairment, ischemic retinopathy and/or age-related macular degeneration, coronary artery disease, blood pressure abnormalities, acute and/or chronic inflammatory disease, mild to moderate depression, seizure, and Parkinsonism. Furthermore, antioxidant, antimutagenic, antigenotoxic, tumoricidal and antioxidant activity of saffron and its ingredient have been found (Abdullaev and Espinosa-Aguirre, 2004).

Antioxidant activity of saffron and its ingredients and management of diabetes

Recent scientific findings have been encouraging, uniformly showing that saffron and its derivatives can affect hyperglycemia in a variety of *in-vivo* and *in-vitro* models, particularly, crocin, crocetin and safranal have significant anti-diabetic activity (Kianbakht et al., 2011). *In-vitro* and *in-vivo* studies have also been designed to evaluate the exact mechanism and effective derivate of saffron against diabetes and its complications. One of the main hypotheses for the modes of saffron and its ingredients (crocin, cocetin and safranal) is inhibitory effect on free radical chain reactions (Assimopoulou et al., 2005; Kanakis et al., 2007; Halataei et al., 2011; Hariri et al. 2010). The useful effects of saffron and its ingredients as an antioxidant in biological systems have been attributed to its capability to stabilize bio-membranes, to scavenge ROS, and to decrease the peroxidation of unsaturated membrane lipids (Papandreou et al., 2011). They have been shown to have a hydroxyl radical scavenging activity (Assimopoulou et al., 2005). It has been shown that the radical scavenging activity of the saffron methanol extract and its constituents, crocin and safranal, is significant, probably because these donate hydrogen atoms for DPPH radical stabilization (Kurechi et al., 1980). Saffron ingredients modulated antioxidant gene expression and upregulate mitochondrial antioxidant genes, leading to a lower mitochondrial oxygen radical generation, which may be responsible at least in part for the improved hyperglycemia, hyperlipidemia and oxidative stress in experimental diabetic model (Hosseinzadeh and Sadeghnia, 2005). These findings were confirmed by variety of studies in which saffron, crocin, crocetin and safranal had protective effects against oxidation induced tissue injuries due to their antioxidant properties. Experimental findings showed that saffron and its ingredients insert anti-genotoxic, tumoricidal and anti-aging through modulating oxidative stress (Premkumar et al., 2003; Samarghandian et al., 2010; Samarghandian et al., 2011; Farahmand et al., 2013). Moreover, antioxidant activities of saffron and its main ingredients played essential role in the treatment of neurodegenerative disorders and related memory impairment, ischemic retinopathy and/or age-related macular degeneration, coronary artery disease, blood pressure abnormalities, acute and/or chronic inflammatory disease, mild to moderate depression, seizure and Parkinsonism in animal modeling (Zhang et al., 1994; Pitsikas et al., 2007; Zheng et al., 2007; Schmidt et al., 2007; Papandreou et al., 2011; Kamalipour et al., 2011; Rahbani et al., 2011; Bharti et al., 2012; Samarghandian and Shabestari, 2013).

Glycemic control and management of diabetes

The hypoglycemic effect of saffron extract seems to be

exerted by mechanisms including stimulation of glucose uptake by peripheral tissues (Yang et al., 2003), inhibition of intestinal glucose absorption (Youn et al., 2004), inhibition of insulinase activity in both liver and kidney (Achrekar et al., 1991), inhibition of endogenous glucose production (Eddouks et al., 2002), inhibition of renal glucose reabsorption (Maghrani et al., 2005) or correction of insulin resistance (Hu et al., 2003) stimulation of β -cells of islets of Langerhans to release more insulin (Xi et al., 2007) regeneration of β -cells islets of Langerhans (Elgazar et al., 2013).

However, possibilities of other mechanisms to exert hypoglycemic effect cannot be rejected. The mechanism of alloxan and streptozotocin (STZ) diabetes has been the subject of many investigations and it is now generally accepted that destruction of the β -cell pancreatic islets is associated strictly with the induction of oxidative and nitrosative stress, both systemically and locally. Therefore, the pancreas is especially susceptible to the action of STZ and alloxan-induced free-radical damage. Many substances have been shown to ameliorate the diabetogenicity of STZ and alloxan in animals by reacting with free radicals formed from STZ and alloxan during its interaction with the β -cell, or prevent radical formation (Jörns et al., 1999). Recently, it was reported that the saffron extract, crocin, crocetin and safranal insert considerable radical scavenging activity and thus antioxidant property (Assimopoulou et al., 2005). Xi et al. (2005) revealed that saffron is used in the traditional medicine in the treatment of diabetes due to its effect in insulin resistance. They also indicated that crocetin has increased insulin sensitivity and ameliorated abnormalities related to insulin resistance such as impaired glucose tolerance, hyperinsulinemia due to high-fructose diet and dexamethasone injection in rats (Xi et al., 2007). This was reported that ethanolic saffron extract (20, 40 and 80 mg/kg) has significant hypoglycaemic effect by increasing the number of β -cells in pancreas and insulin plasma level and reaction with free radicals in alloxan induced diabetic rat (Mohajeri et al., 2009). Another study also demonstrated that saffron extract has hypoglycemic effects on healthy male rats. It extract could increase their insulin secretion from pancreatic β -cells (Arasteh et al., 2010). An *in-vitro* model study indicated that saffron strongly enhanced glucose uptake and the phosphorylation of AMP-activated protein kinase (AMPK)/acetyl-CoA carboxylase (ACC) and mitogen-activated protein kinases (MAPKs); AMPK plays a major role in the effects of saffron on glucose uptake and insulin sensitivity in skeletal muscle cells (Kang et al., 2012). Oral administration of saffron extract at the three different doses 200, 400 and 600 mg/kg caused significant increase in serum insulin level in all treated diabetic rats, while significantly reduced blood glucose levels. In addition, saffron extract (600 mg/kg) improved hypertrophy and hyperplasia of β -cells of islets of Langerhans associated

with pyknosis of their nuclei in alloxan induced diabetic rats (Elgazar et al., 2013).

Administration of crocin significantly reduced the blood glucose level in diabetic animals (Rajaei et al., 2013; Shirali et al., 2013; Tamaddonfard et al., 2013). In experimental model of DM also observed that safranal (0.25, 0.5 and 0.75 mg/kg/day for 4 weeks) administration led to a significant decrease in glucose, MDA and NO content accompanied by a significant increase in plasma GSH content and CAT and SOD activities. This finding indicated that safranal exerts anti-hyperglycemic and hypoglycemic properties by modulation of oxidative stress in STZ diabetic rats (Samarghandian et al., 2013). Also, kianbakht et al. (2011) confirmed antihyperglycemic activity of saffron, crocin and safranal in alloxan diabetic rats. The findings of one study indicated that saffron and its main ingredients (crocin, crocetin and safranal) may have anti-hyperglycemic and blood insulin level elevating effects without hepatic and renal toxicities in the alloxan-diabetic rats (kianbakht et al., 2011). Based on these results, the protective effect of saffron extract on pancreas of diabetic rats might be attributed directly to scavenging activity due to its major constituents including crocin, crocetin and safranal. These compound as natural antioxidant may be very important in mitigating impaired insulin secretion and action in insulin resistance and prevent diabetes complications

Dislipidemia control and arthrosclerosis management

Dyslipidaemia describes a group of conditions in which there are abnormal levels of lipid and lipoprotein in the blood (Bhalodia et al., 2010). The level of serum lipid fractions is often increased in DM and such an elevation plays a major role in coronary artery disease. This abnormal high level of serum lipid fractions is mainly due to the decrease in the action of lipolytic hormones in the adipocyte tissue. Under normal circumstances, insulin activates the enzyme lipoprotein lipase, which hydrolysis triglycerides. However, insulin deficiency or insulin resistant in diabetic patients leads to hypertriglyceridemia and hypercholestermia by inactivating lipoprotein lipase (Sharma et al., 2003).

Diabetes mellitus usually includes lipid abnormalities such as elevated circulating levels of TG, TC, LDL-C and usually accompanied by decreased circulating levels of HDL particles (Sharma et al., 2003). During diabetes, persistent hyperglycemia causes increased production of free radicals, especially reactive oxygen species (ROS). Lipids when react with free radicals, they undergo peroxidation to form lipid peroxides. The increase in the level of ROS in diabetes could be due to their increased production and/or decreased destruction by nonenzymic and enzymic catalase (CAT), reduced glutathione (GSH),

and superoxide dismutase (SOD) antioxidants (Logani and Davis, 1979). These findings may constitute the predominant mechanism in STZ and alloxan induced complications of hyperglycemia. Several mechanisms for the hypolipidemic effects of saffron extract and its constituents have been suggested: (1) modulatory effects on the oxidant-antioxidant system (Xiang et al., 2006); (2) inhibitory effect on pancreatic lipase. It may act by reducing the absorption of fat and cholesterol through inhibiting pancreatic lipase activity (Sheng et al., 2006). In several studies, treatment animals with different concentrations of saffron showed improved lipid profile (Elgazar et al., 2013). Regarding the hypolipidemic effects of saffron, Xu et al. (2005) reported that in experimental hyperlipemic rats with 2 months feeding of heavy cholesterol, crocin decreased largely the content of cholesterol, triglyceride and density lipoprotein in blood and increased the content of high-density lipoprotein. In agree with this result, Sheng et al. (2006, 2008) indicated that crocin has lipid lowering properties and selectively inhibits the activity of pancreatic lipase as a competitive inhibitor. Moreover, He et al. (2005) found that crocin has a potent hypotriglyceridemic and hypocholesterolemic activity in atherosclerotic quails. Shirali et al. (2013) also showed that crocin significantly decreased the levels of triglyceride, total cholesterol, and low-density lipoprotein and increased the high-density lipoprotein in the diabetic rats by improving insulin resistance in the diabetic rats. Other investigations indicated that crocetin has increased insulin sensitivity and ameliorated abnormalities related to insulin resistance such as impaired glucose tolerance, hyperinsulinemia, dyslipidemia and hypertension due to high-fructose diet, high fat diet and dexamethasone injection in rats (Xi et al., 2005, 2007a; Shang et al., 2008). Crocetin attenuated the palmitate-induced insulin insensitivity in the rat adipocytes (Xi et al., 2007b).

The antioxidant effects of crocetin may, at least in part, explain the ability of this compound to attenuate insulin insensitivity. In addition, Samarghandian et al. (2013), indicated that safranal inhibits elevation of the serum lipid level by controlling oxidative and nitrosative systems. Lipids change to form lipid peroxides when it reacts with free radicals. Lipid peroxides decompose to form numerous products including malondialdehyde (Raghuvanshi et al., 2007). The toxicity of oxygen, or of its radical derivatives, is often accompanied by the peroxidation of lipids. Lipid peroxidation as induced by low-level exposures to nitrogen dioxide appears to proceed either by hydrogen atom abstraction or by nitrogen dioxide addition to the olefin. These abnormalities may be further exacerbated by the increased oxidizing environment which enhances the formation of oxidized LDLs (ox-LDLs), glycated LDL and oxysterols (formed from the oxidation of cholesterol). It has been suggested that these oxidized lipid products can bind to specific receptor proteins or activate inflammatory proteins which generate ROS

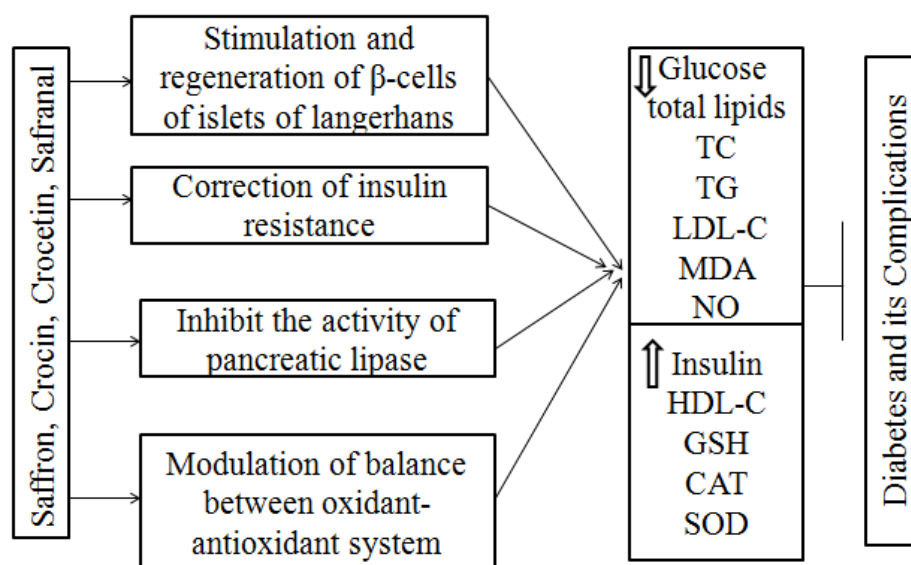


Figure 2. The molecular targets of diabetes and its complications modulated by saffron and its main ingredients.

(Johansen et al., 2005). The import of ox-LDLs in the vascular wall is an important mechanism by which ROS and oxidative stress induce atherosclerosis. Crocetin could also prevent progression atherosclerosis by inhibition adhesion of leukocytes to the bovine aortic endothelial cells (BEC) induced by advanced glycation end products (AGEs) and AGEs-induced BEC apoptosis possibly through its antioxidant activity and thus it has been suggested that crocetin may prevent diabetes-associated vascular complications (Xiang et al., 2006a, 2006b). Increasing evidence suggests that oxidative stress and changes in nitric oxide formation or action plays major roles in the onset of atherosclerosis. Samarghandian et al. (2013) also indicated that safranin might prevent the occurrence of atherosclerosis by reduction of serum NO content. Therefore, saffron and its main ingredients are beneficial for curing of atherosclerosis by controlling lipid profile through correction of insulin resistance, oxidant-antioxidant system and inhibition pancreatic lipase. Table 1 shows some studies that evaluate the effect of saffron, crocin, crocetin and safranin on glucose and lipid profile in diabetic model and proposed mechanisms. Figure 2 indicates the molecular targets of diabetes and its complications modulated by saffron, crocin, crocetin and safranin.

CONCLUSION

This review highlights the effects of saffron and its main ingredients on various parameters of diabetes including unveiling potential biochemical pathways involved. Saffron

extracts influence the content of free radicals and antioxidants in treated animals, suggesting that the levels of free radicals and antioxidants are associated with the diabetic state. Saffron and its main ingredients, in addition to reducing blood glucose level in diabetic rats, lead to an increase of GSH, CAT, GST and SOD whose activities used to be decreased by diabetic conditions.

Scientists worldwide are more attracted to show that consumption of saffron positively correlates with a lower risk of diabetes and its complications, and they also studied the attribution of the large number of phytochemicals in saffron. Among these phytochemicals, crocin, crocetin, and safranin are considered the most medicinally bioactive and the most frequently examined in many *in vitro* and *in vivo* studies. Different hypotheses for the mode of antidiabetic action of saffron and its ingredients have been suggested and in detail discussed in this review. Several studies suggested that hypoglycemic and hypolipidemic effects of saffron and its main components seem to exert mechanisms including stimulation of glucose uptake by peripheral tissues inhibition of intestinal glucose, absorption inhibition of insulinase activity in both liver and kidney, inhibition of endogenous glucose production, inhibition of renal glucose reabsorption or correction of insulin resistance stimulation of β -cells of islets of Langerhans to release more insulin regeneration of β -cells islets of Langerhans.

Recently, many studies have shown that saffron and its main ingredients ameliorated the diabetogenicity of STZ and alloxan in animals by reacting with free radicals formed from STZ and alloxan during its interaction with the β -cell, or prevent radical formation.

Table 1. Effect of saffron, crocin, crocetin and safranal on glucose and lipid profile in diabetic model and proposed mechanisms.

Saffron and its ingredients	Cell lines/Animal models	Effect	Mechanism of action	References
Saffron extract	Alloxan diabetic rat	Serum glucose, TG and TC Serum insulin	Increased the number of β -cells in pancreas, modulation of balance between oxidant-antioxidant system	Mohajeri et al. (2009), Kianbakht et al. (2011), Elgazar et al. (2013)
	Skeletal muscle cell	Glucose uptake in muscle cells	Phosphorylation of AMPK muscle cells, regeneration of β -cells of islets of Langerhans	Kang et al. (2012)
Crocine	Alloxan and STZ diabetic rat	Serum glucose, MDA, TG, TC and LDL-C GSH and HDL-C	Modulation of balance between oxidant-antioxidant system, correction insulin resistance, inhibition of the activity of pancreatic lipase	He et al. (2005), Xu et al. (2005), Sheng et al. (2006), Kian bakht et al. (2011), Rajaei et al. (2013), Shirali et al. (2013), Tamaddonfard et al. (2013)
Crocetin	Fructose-fed rat, high-fat diet rat dexamethasone- exposed rat	Serum glucose, TG and TC Serum insulin	Stimulation and regeneration of β -cells of islets of Langerhans, correction insulin resistance, modulation of balance between oxidant-antioxidant system	Xi et al. (2005, 2007a, b), Sheng et al. (2008)
	Bovine aortic endothelial cell	Inhibition adhesion of leukocytes to the bovine aortic endothelial cells and prevent progression atherosclerosis	Modulation of balance between oxidant-antioxidant system	Xiang et al. (2006a, b)
Safranal	Alloxan and STZ diabetic rat	Serum glucose, total lipids, TC, TG, LDL-C, MDA and NO Serum insulin, HDL, GSH, CAT and SOD	Modulation of balance between oxidant-antioxidant system	Kianbakht et al. (2011), Samarghandian et al. (2013)

To date, the exact mechanism of antidiabetic effect of saffron is not clear. However, the most medicinally bioactivity of saffron belongs to carotenoids. Carotenoids exhibit biological activities as antioxidants, and act as a membrane-associated high-efficiency free radical scavenger. Several studies pointed out the use of some of them, such as crocin, crocetin and safranal, in diabetic management. These compounds are lipid-soluble and might act as free-radical scavengers, and prevent protein, lipid and carbohydrate oxidation.

In conclusion, this review proposes that the antidiabetic activity of saffron and its compounds is more closely related to the antioxidant reinforcement, rather than to other possible mechanisms. However, present findings have not yet been verified by clinical trials in humans and

in-depth studies need to define the efficacy of saffron in diabetic management. In addition, the possible long-term toxic effects of saffron extract and protective effects of different doses also need to be determined.

Conflict of interest

The author(s) confirm that this article content has no conflicts of interest.

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