A review of the anti-diabetic potential of saffron

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ABSTRACT: Diabetes mellitus is one of the most prevalent metabolic disorders that affect people of all genders, ages, and races. Medicinal herbs have gained attention from researchers and have been widely investigated for their antidiabetic potential. Saffron (*Crocus sativus* L.) and its main constituents, that is, crocin and crocetin, are natural carotenoid compounds, widely known to possess a wide spectrum of properties and induce pleiotropic anti-inflammatory, anti-oxidative, and neuro-protective effects. An increasing number of experimental, animal and human studies have investigated the effects and mechanism of action of these compounds and their potential therapeutic use in the treatment of diabetes. This narrative review presents the key findings of published clinical studies that examined the effects of saffron and/or its constituents in the context of diabetes mellitus. Moreover, an overview of the proposed underlying mechanisms mediating these effects, the medicinal applications of saffron, and the new findings regarding its effect on diabetes and various cellular and molecular mechanisms of action will be debated.

KEYWORDS: Saffron, *Crocus sativus* L., crocin, crocetin, diabetes mellitus, antioxidant

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Introduction

Diabetes mellitus (DM) is one of the most prevalent metabolic disorders and is known as a critical public health issue with noticeable consequences for human life and health expenditures.[1,2] Each year over 1 million deaths can be ascribed to diabetes alone, making it the ninth leading cause of death.[3] Prolonged uncontrolled DM causes several micro and macrovascular complications, for instance, nephropathy, retinopathy, neuropathy, cardiovascular disease and stroke. Optimal control of blood glucose and lipid concentrations can decrease the incidence of DM-related complications; however, glycemic control is a constant challenge for diabetic patients. Drug therapy and lifestyle modifications such as dietary changes are strategies to modify blood glucose.[4] Herbal and natural medicine has been widely investigated for alternative treatment options. There is a growing body of literature addressing the use of herbal supplements in the management of diabetes. Saffron (*Crocus sativus* L.) has become a natural product of high interest since studies have shown promising effects of which on glycemic control. In vitro and in vivo studies as well as clinical trials have indicated that saffron and its constituents have antidiabetic, hypolipidemic, anti-hypertensive effects.[5-7] This review aimed to summarize the recently published evidence regarding the role of saffron and its bioactive components in DM.

Antidiabetic Medication: From Chemical Drugs to Herbs

Various drugs are used to lower the plasma glucose in patients with DM. Insulin is widely used among patients with type 1 DM as well as type 2 DM patients with uncontrolled diabetes despite optimal oral glycemic therapy.[8] Type 2 diabetes medications usually act through mechanisms such as enhancing insulin secretion, stimulating its function, or reducing glucose production in hepatocytes.[1] Some of these drugs include biguanides (Metformin), sulfonylureas (Gliclazide), dipeptidyl peptidase-4 (DPP-4) inhibitors (Sitagliptin), SGLT2 inhibitors (Empagliflozin), glucagon-like peptide-1 (GLP-1) receptor agonists (Liraglutide), and thiazolidinediones (Pioglitazone).[9] Some of these antidiabetic agents may cause side effects. Signs of congestive heart failure, fluid retention and bone fractures were observed in a group of patients treated with thiazolidinediones.[10,11] Other drugs like biguanides, DPP-4 inhibitors and SGLT2 inhibitors can cause complications like lactic acidosis, nasopharyngitis and urinary tract infections, respectively.[12] This led researchers to seek alternative therapies.

Using herbal medicine to treat various diseases has a long history in different regions all around the world.[13] The numerous effects of these medicinal plants and the extracted compounds have been indicated in many studies. In case of diabetes there are evidences that type 2 diabetes mellitus was regarded as a major "Xiao-Ke disease" in ancient Chinese books and

Chinese have used herbal medicines as treatment to the diseases for more than 1500 years.[14] Nowadays, there are numerous studies which attempted to find out the beneficial effects of herbal medicine on controlling the complications of diabetes and improving the outcome of patients.[14-17]

The most common and effective antidiabetic herbs of Indian origin are bael (*Aegle marmelose*), Babul (*Acacia arabica*), onion (*Allium cepa*), garlic (*Allium sativum*), ghrita kumara (*Aloe vera*), church steeples (*Agrimonia eupatoria*), neem (*Azadirachta indica*), and ash gourd (*Benincasa hispida*).[18] Ginseng, Bitter melon, Golden Thread, Fenugreek, Garlic, and Cinnamon have been recommended in traditional Chinese medicine.[19] Several studies have also evaluated the anti-diabetic effects of spices such as cinnamon,[20] cardamom,[21] ginger,[22] cumin, black seed,[23] and saffron (*Crocus sativus* L).[24]

Here in this article, we are going to review the studies on the anti-diabetic antidiabetic effects of saffron one of the most famous Iranian spices.

Saffron (*Crocus sativus* L)

Saffron, one of the most expensive spices, is usually grown as a perennial crop. The crimson-colored stigmas of saffron are used as a spice. Saffron has antitumor, anti-inflammatory, and andepressant properties. It also is used to several diseases such as diabetes, several types of cancers, and Alzheimer's disease.[25] Saffron is known as an ancient spice. Besides its medicinal effects saffron is used for dyeing and as a food spice. Saffron is cultivated in different countries such as Iran, India, Spain, Afghanistan, Greece, and Italy. Iran produces 90% of the world saffron.[26]

Saffron contains various compounds including vitamins, minerals, carbohydrates and protein, flavonoids, and anthocyanin. The major saffron compounds are safranal, picrocrocin, crocin, and crocetin. Crocin and crocetin are 2 carotenoid compounds of saffron. crocin is responsible for the red color of saffron and composes the 6% to 16% total dry matter of saffron based on the types of methods that are produced.[27] The antihypertensive effect of safranal, and crocin have been proved in vivo.[28] Crocin has also shown anti diabetic and lipid lowering effects.[29] Crocin and safranal have also shown showed high antioxidant properties.[30]

Methods

In order to extract relevant articles, we performed a thorough search in several databases such as PubMed, Web of Science, Scopus, Google scholar and Central. The keywords included "Saffron," "*Crocus Sativus* L," "Crocin," "Crocetin," "Diabetes mellitus," and "Antioxidant." The English language articles up to January 2022 were extracted through title and abstract screening. The duplicate articles were removed using Endnote X9. Hence the relevant articles were reviewed.

In Vitro Studies

Dehghan et al Conducted a study to investigate the effect of saffron consumption on diabetes. The findings showed that saffron consumption decreases triglyceride, low-density lipo-protein (LDL), very-low-density lipoprotein (VLDL), glycated hemoglobin levels, and could also increase insulin sensitivity by further expression of GLUT4 (Glucose transporter type 4), and AMPK (AMP-activated protein kinase). This effect was dose-dependent and more effective at higher doses. They also found that higher doses of saffron could increase insulin secretion and glucose uptake by affecting RIN-5F cells.[31] In a study by Kang et al, similar results were obtained on skeletal muscle cells. They found that saffron is involved in increasing glucose uptake in muscle cells via AMPK and PI3 kinase (phosphatidylinositol 3-kinase)/Akt (also known as protein kinase B) pathways.[6]

About 100 different substances are obtained from saffron.[32,33] These substances have different effects on human body and some can play an anti-diabetic role; however, the mechanism of action is not yet fully understood. Wali et al studied the anti-diabetic, antioxidant, and antibacterial effects of saffron and its derivates. These compounds (most importantly flavonoids and terpenes) showed anti-diabetic effects by inhibiting the α-glucosidase enzyme. It was also shown that saffron has antibacterial and antioxidant effects in a dose-dependent manner.[34]

Saffron can also treat the complications of diabetes. Although the mechanism which glucose leads to neurotoxicity has not been fully elucidated, one of the possible explanations is the increase of reactive oxygen species (ROS) production. Mousavi et al found that saffron, especially crocin (one of the most important compounds in saffron as mentioned earlier), could reduce the effects of diabetic neuropathy by reducing ROS.[35] In another study, Yang et al realized that crocin has neuroprotective effects exerted through activating the PI3 kinase/Akt pathways and can also help to treat diabetic retinopathy by suppressing oxidative stress and pro-inflammatory response in microglial cells.[36] Table 1 summarizes the main findings of the in vitro studies on the anti-diabetic potential of saffron.

Animal Studies

Previous findings have confirmed that components of saffron extract including saffron petal extract and crocin have a high antioxidant capacity.[30,61,62] Various articles referred to the antioxidant effects of saffron as the main mechanism for its beneficial effects on diabetic animals.[40,45,49,51,53,54,56,58]

Oxidative stress (OS) in uncontrolled hyperglycemia is known to have a fundamental role in pancreatic dysfunction and liver injury. The leading components of the intrinsic anti-oxidation system in the tissues are superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase.[50] In this regard, Yaribeygi et al studied the potential of Crocin, a pharmacologically active component of *Crocus sativus* L., to improve the antioxidant defense systems of pancreatic and hepatic cells. The results showed that Crocin boosted the antioxidant defense system by enhancing the enzymatic activities of both SOD and catalase and can decrease the oxidative stress by decreasing malondialdehyde (MDA) production (as the main indicator of OS) in pancreas and liver tissues of the diabetic-treated rats.[49,56] Another mechanism of Saffron products to im-prove the antioxidant status is by reducing lipid peroxidation.[63] Saffron is reported to inhibit lipid peroxidation and restore SOD activity.[64,65] In a study conducted by Rajaei et al the levels of total thiol (SH) groups, a sensitive component to oxidative damage, and thiobarbituric acid reactive substance (TBARS), an index of lipid peroxidation, were assessed in the kidney and liver of STZ (Streptozotocin)-induced diabetic rats. Their findings suggested that crocin has anti-oxidative effects, contributing to the decrease of lipid peroxidation in diabetic animals, and may be useful in the management of diabetes.[45]

Hypoglycemic and hypolipidemic effects of saffron, as a result of its antioxidant, anti-inflammatory, and apoptosis regulatory potential, have been confirmed in different studies. Samaha et al performed a comparative study about the effects of crocin and sitagliptin (a standard oral hypoglycemic medication) in STZ-induced diabetic rats. The results showed that crocin had a greater effect compared to sitagliptin on serum glucose level, insulin immune-reactivity, and β-islets diameter.[29,37,51] Physical activity is another method of diabetes management. Different kinds of activities including aerobic and resistance exercises, along with saffron consumption, are reported to have synergistic effects on improving diabetic parameters in rats. These effects are exerted via preventing excessive apoptosis of the pancreatic beta-cells associated with type DM and antioxidant mechanisms.[31,52,66]

DM patients suffer from hyperglycemia, dyslipidemia, and insulin resistance caused by abnormal metabolism which leads to many micro and macro vascular complications.[67] Saffron has been investigated in multiple in vivo studies for alleviation of diabetic complications.[53,54,58] One of its complications is diabetic nephropathy, one of the main causes of death in DM patients.[68] In a recent study performed by Qiu et al the hypoglycemic and renal protection properties of crocin-I (CR) was demonstrated by the regulation of potential indicators of nephropathy. They reported hypoglycemic, hypolipidemic, and renal protective effects of CR in diabetic mice.[53]

Diabetic encephalopathy is another severe complication in diabetic patients. The findings of a study by Samarghandian et al indicated that treatment with Saffron ameliorated oxidative stress in the hippocampus of diabetic rats and improved diabetic encephalopathy and cognitive deficits.[58] In diabetic rats, after consuming saffron extract, changes in blood sugar occurred, which included a decrease in fasting blood sugar, and a reduction of hyperglycemia in a high dose of saffron consumption combined with metformin. An increase in serum insulin levels and insulin secretion were also observed.[5,38,39,46-48,50,69,70] Saffron extract affects lipid profile by reducing the level of total cholesterol, blood triglyceride level, and VLDL.[5,38,47,69-71] Adiponectin and HDL-C are increased and the LDL / HDL ratio decreased overall improvement in lipid profile was observed.[46,69-71] Consumption of saffron extract prevented weight loss in mice treated with saffron compared to diabetic mice[38,71] Weight gain has also been observed in studies.[72] Consumption of saffron extract in diabetic male mice reduces OS, infection, (interleukin) IL-1β levels superoxide dismutase, Malondialdehyde, and thiobarbituric acid-reactive substances. Also, the consumption of saffron, metformin, and the combination of them can improve learning and memory disorders and anti-apoptotic mechanisms.[44,46,47,57,71] Pancreatic tissue function improved after consuming saffron extract and returned to normal. Many studies demonstrated that saffron extract has positive effects such as improving kidney tissue, reducing creatine, BUN (blood urea nitrogen) serum, immuno-expression of xanthine oxidase (XO) activities, glutathione (GSH) contents, and caspase-3.[38,39,44,46] Kakouri et al used crocin isolated from *Crocus sativus* L to investigate its effects on the pancreatic beta cell of zebrafish. Embryos of zebrafish were exposed to an aqueous solution containing saffron; then, they measured glucose levels of the whole embryos. The results showed glucose levels of the zebrafish embryo decreased, and expression of insulin and phosphoenolpyruvate carboxykinase 1 (pck1) increased. It was concluded that crocin may have roles in the metabolism of glucose and insulin management.[55] Majidi et al[60] performed an experiment on 40 male diabetic rats to evaluate the effect of damask rose petals, saffron petals, and saffron-damask rose petal herbal teas in inflammatory factors, fasting blood sugar, weight loss, and lipid profile. In 3 intervention groups, saffron petals, damask rose petals and saffron petals along with damask rose petals, in comparison with the normal group, a decrease in weight, hba1c, and an increase in IGF-1 were observed. Along with a decrease in FBS, LDL, HDL. In the saffron petal group. In another study by Keelo et al, it was found that crocin exerts protective effects on the diabetic nephropathy. This study also showed that saffron can lower blood sugar and blood triglycerides and suppress reduced TGF-β1 and oxidative stress in the kidneys. In addition, crocin a protected renal architecture against the development of renal fibrosis and reduced BUN and creatinine.[59]

Table 1 summarizes the main findings of the in vivo studies on the anti-diabetic potential of saffron.

Clinical Trials

Several studies investigate the effects of alcoholic extraction of saffron (*Crocus sativus* L) on depression, anxiety, sleep quality, and life satisfaction in type 2 diabetes mellitus (T2DM) patients. Milajerdi et al designed a double-blinded, randomized, and placebo-controlled clinical trial. Participants in this study were outpatients who suffered from mild to moderate Comorbid Depression-Anxiety (CDA). The results showed that mild to moderate Comorbid Depression-Anxiety (CDA), sleep disturbance, and anxiety were alleviated considerably in the patients who consumed saffron capsules compared to the control group. however, depression alone was not relieved.[73] In other studies, Dehghanmehr et al reported that daily saffron consumption can improve sleep quality in diabetic patients and have a beneficial effect on their anxiety levels.[31,74] In another study conducted by Tajaddini et al to investigate the relationship between saffron consumption and quality of sleep and life, they concluded that saffron in DM patients is associated with improved sleep and quality of life.[75]

Table 1. In vitro and in vivo studies on the anti-diabetic potential of saffron.

IN VITRO/ANIMAL TRIALS/DOSAGE	RESULTS	REFERENCES
Effect of Saffron Extract and Crocin on PC12 cells.	It decreased the cell viability of PC12 after 4 days and increased the glucose-induced toxicity in PC12 cells mediated by ROS production partly.	Mousavi et al[35]
Different effects of *Crocus sativus*.	It can inhibit the growth of numerous cancer cells and have antidiabetic, antimicrobial, and α-glucosidase inhibitory activity.	Wali et al[34]
The action of Crocin on microglial cells	Crocin decreases microglial activation after traumatic brain injury and can prevent oxidative stress.	Yang et al[36]
Role of saffron on glucose rate in skeletal muscle cells	Saffron strongly enhanced glucose uptake and the phosphorylation of AMPK, ACC, and MAPKs. It can also induce (dependent on time- and dose) the increase of AMPK phosphorylation in C2C12 cells.	Kang et al[6]
Saffron impacts on GLUT4/AMPK	Saffron can stimulate AMPK and GLUT4 via redox-mediated mechanisms. It also has been shown that the more dosage of saffron causes more glucose uptake. Saffron intensely stimulates phosphorylation in AMPK and GLUT4 cell lines.	Dehghan et al[31]
Adult male Sprague-Dawley rats divided into 4 groups: normal control group (G1) received distilled water for 4 weeks and 3 groups injected with STZ (50 mg/kg, IP (intra-peritoneal)) received distilled water (G2), sitagliptin (10 mg/kg, orally) (G3) and crocin extract of saffron (10 mg/kg, orally) (G4) for 4 weeks.	Crocin and sitagliptin prevented blood sugar spikes. Crocin and sitagliptin significantly reduced serum glucose (Crocin was more effective than sitagliptin). serum glucagon and suppressed pancreatic caspase-3 and CD68 expression. Also, body weight and serum insulin increased after 4 weeks of treatment.	Samaha et al[37]
Adult male Wistar rats (weight 150-200 g) divided into 6 groups: normal control group (G1) received distilled water(1 ml) and 5 groups injected with STZ (60 mg/kg, ip) received orally distilled water(1 ml), Hydroethanolic extracts of tepal (250 mg/kg/day), stigma (50 mg/kg/day), leaf (250 mg/kg/day) of crocus and glibenclamide (2 mg/kg/day) (G6) for 21 days.	The glibenclamide and Hydroethanolic extract of tepals, stigmas, and leaves decreased blood glucose levels, plasma total cholesterol, plasma triglycerides, and plasma creatinine in the treated diabetic rats compared with the untreated. Also, glibenclamide and Hydroethanolic significantly can protect rats against weight loss.	Ouahhoud et al[38]
Adult male Albino mice (25-30 g each) divided into 4 groups: control (G1), saffron(G2), untreated diabetic group(G3), and diabetic rats that received aqueous saffron extract (ASE) (80 mg/kg BW) (G4) for 45 days.	The saffron aqueous extract was significantly reduced the blood glucose levels of the treated diabetic group (G4). Also, the untreated diabetic group (G3) exhibited significantly increased serum glucose.	Nassar et al[39]
Adult male Wistar rats (Weight 225 ± 25 g) divided into 5 groups: normal control group (G1) received normal saline(1 ml) for 21 days and 4 groups injected with STZ (60 mg/kg, ip) received ethanolic extract of saffron stigma extract (SSE) 25 mg/kg (G2) and 100 mg/kg (G3), Normal saline(1 ml) (G4), glibenclamide (0.6 mg/kg) (G5).	Significant reduction in serum glucose, MDA level, G6Pase, and glucokinase gene (GK) expression after treatment with SSE (especially in high dose). SSE in specified doses increased β cell counts results in an increased level of insulin.	Motamedrad et al[40]
Adult male C57BL/6 mice were divided into 3 groups (n = 10): Healthy mice(G1), untreated diabetic mice(G2), treated diabetic mice that received The hydroalcoholic extract of saffron (500 mg/kg, orally) (G3) for 3 weeks.	The hydroalcoholic extract of saffron was significantly reduced the blood glucose, triglyceride, and cholesterol levels of diabetic mice(G3).	Faridi et al[41]
Male Wistar rats (weight = 309.91 ± 29.68) divided into 5 groups: normal control group (G1) received citrate buffer solution for 2 weeks, diabetic control group (G2), diabetic aerobic exercise group (G3), treated diabetic group (G4), and treated aerobic exercise group (G5). Treated rats received daily 25 mg/kg hydro extract of saffron for 2 weeks.	glucose and cholesterol Serum levels were significantly decreased in diabetic rats that were used saffron extract along with aerobic exercise compared to the diabetic control and normal control groups. However, no change was seen in free fatty acids, serum triglycerides, insulin, and insulin resistance in any group.	Iraji et al[42]
male Sprague–Dawley rats(250 g) divided into 2 groups: A) 5 groups injected with STZ (55 mg/kg, ip): 1) control, 2) training, 3) extract treatment, 4) training + extract treatment 5) treated with metformin 100 mg/kg B) non-diabetic group: 1) control, 2) training, 3) extract treatment 4) training + extract Treated rats received a hydroalcoholic extract of saffron at 40 mg/kg daily for 6 weeks.	Significant reduction in serum glucose, insulin resistance, HbA1c39, triglyceride, LDL, and VLDL levels in treated rats compared to untreated after 6 weeks.	Dehghan et al[31]
Adult male Sprague-Dawley rats (200-220 g) divided into 9 groups: one normal control group received 0.9% saline and 8 groups injected with STZ (60 mg/kg, ip) received the hydroalcoholic extract of jujube (25 mg/kg (G1), 100 mg/kg (G2)), hydroalcoholic extract of saffron (G3, G4), hydroalcoholic extract of barberry (25 mg/kg (G5), 100 mg/kg (G6)), quercetin (15 mg/kg, ip) (G7), 0.9% saline (G8) for 14 days.	That serum levels of triglyceride, VLDL, and FBS decreased and adiponectin level increased significantly in all treated groups. In conclusion, Jujube could increase significantly HDL-C but other plant extracts did not affect cholesterol.	Hemmati et al[43]

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Table 1. (Continued)

IN VITRO/ANIMAL TRIALS/DOSAGE	RESULTS	REFERENCES
Female Wistar albino rats(150-200 g) divided into 3 groups: one normal control group (G1) injected 1 ml sodium citrate buffer intraperitoneally and received normal saline (5 ml/kg) and 2 groups injected with STZ (60 mg/kg, IP) that also received normal saline (5 ml/kg) (G2) and crocin extract of saffron dissolved in normal saline (20 mg/kg/day) (G3) for 21 days.	Significant reduction in MDA level, XO activities, and elevated GSH contents in the treated diabetic group (G3). Also, crocin slightly decreased the high level of plasma Cr and BUN.	Altinoz et al[44]
Neonatal male Wistar rats were randomly divided into five groups: the control group (G1), the control group that received a higher dose of crocin (G3), and 3 groups injected with STZ (90 mg/kg, IP). One control diabetic group(G3) and two treated diabetic groups received crocin that was extracted from saffron (50 mg/kg (G4) and 100 mg/kg (G5)) for 5 months.	Significant reduction in serum glucose, AGE, HBA1c, LDL, TG, fasting insulin levels, and a significant increase in HDL level in rats treated with crocin compare with the untreated group was seen. But no significant difference was observed between the two doses of crocin.	Shirali et al[29]
Male Wistar rats divided into 5 groups: one normal control group received normal saline (G1) and 4 groups injected with STZ (55 mg/kg, IP) received normal saline (G2), crocin at doses of 15 mg/kg (G3), 30 mg/kg (G4) and 60 mg/kg (G5) for 6 weeks.	After 6 weeks, the serum glucose level of G4 and G5 decreased but G3 serum glucose levels had no change. TBARS levels in the liver and kidney significantly decreased at the dose of 30 and 60 mg/kg compared with the diabetic control group (G2) and the total thiol concentration of liver increased in the treated diabetic group (G3, G4, G5) compare with the control group, but the total thiol concentration of kidney didn't change.	Rajaei et al[45]
35 male albino rats of Sprague-Dawley strain were divided into five groups: Normal control group (G1), diabetic control group (G2) and treated diabetic groups received orally saffron at levels of 200 mg/kg (G3), 400 mg/kg (G4), and 600 mg/kg (G5) for 4 weeks.	body weight and serum insulin level in all treated diabetic groups significantly increased while significantly reduced blood glucose levels as well as the improvement in lipid profile and liver (ALT, AST, ALP) and kidney (BUN, UA, Cr) functions compared to the positive control group.	Elgazar et al[46]
30 male Wistar rats divided into 5 groups One negative control group fed on a normal laboratory diet and 4 groups injected with STZ (40 mg/kg, IP) were fed a High fat (HF) diet as the positive control (G2), a High-fat diet enriched with pure saffron (S) at a level of 0.08% (G3), a high-fat diet enriched with rye bread (RB) (G4), a high-fat diet with rye bread fortified with 0.12% saffron (RB + S) (G5) for 5 weeks.	significant reduction in TBARS concentration, TG, FBG levels after S(G3), RB(G4), *S* + RB(G5) treatment. Also, incorporation of S, RB, or RB + *S* into the HF diet led to significantly increased blood insulin levels in comparison to the control STZ-induced rats.	Bajerska et al[47]
Male adult Wistar rats divided into 11 groups: two healthy control groups received physiological saline (G1) and 10% DMSO in physiological saline (G2) And 9 groups injected with alloxan (125 mg/kg, IP) received physiological saline (G3), 10% DMSO in physiological saline (G4), saffron extract at the dose of 80 mg/kg (G5) and 240 mg/kg (G6), crocin of saffron at the dose of 50 mg/kg (G7) and 150 mg/kg (G8), safranal (an organic compound isolated from saffron) of saffron at the dose of 0.25 ml/kg (G9) and 0.5 ml/kg (G10), glibenclamide (G11) respectively for 6 weeks.	Compare with control diabetic rats there was a significant reduction in blood glucose and blood HbA1c levels and significant elevation of the blood insulin level of the diabetic rats that received saffron extract, crocin, safranal, and glibenclamide. Also, crocin, safranal, and glibenclamide did not have any significant effects on the blood SGOT, SGPT, and creatinine levels in diabetic rats.	Kianbakht and Hajiaghaee[48]
Male Wistar rats were accidentally separated into four groups including control, normal treated, diabetic, and diabetic treated. control and diabetic groups were handled by crocin (the chemical primarily responsible for the color of saffron.) 40 mg/kg/day for 8 weeks. The animals were victimized to delete liver tissues.	However, crocin markedly decreases blood glucose in the diabetic-treated group, STZ infusion markedly enhanced blood glucose. In the diabetic group, crocin markedly, decrease MDA and nitrate amount but enhanced CAT and SOD enzyme activity.	Yaribeygi et al[49]
Rats were separated into Control, Diabetes, Safranal, and Metformin groups. STZ was administered at the first. Low doses mixture of chemicals containing metformin and Safranal were imported after verification of diabetes on days 3 and carried on for 37 days. Memory and acquisition tested by using MWM on days 40-45	Safranal and metformin had no traces, whereas their low dose mixture remedy markedly decreases STZ contained hyperglycemia.	Delkhosh-Kasmaie et al[50]
rats were divided into the following groups: control, untreated diabetic, and three saffron extract-treated diabetic groups. Diabetes was induced by STZ in rats. Saffron was administered 3 days after STZ administration and carried on a total of 4 weeks.	in the saffron-treated diabetic group saffron markedly reduced blood glucose, triglycerides, nitric oxide, total lipids, malondialdehyde, cholesterol levels and increase the glutathione level, superoxide dismutase, and catalase activities. The outcomes accredit using saffron as a cure against diabetes mellitus and its vascular problems.	Samarghandian et al[51]
Animals were separated into the following groups: control, diabetes, diabetic-crocin, diabetic-voluntary exercise, diabetic-crocin-voluntary exercise. Type 2 diabetes is enforced for 4 weeks by a high-fat diet and with the infusion of STZ. Animals received crocin orally and the voluntary exercise administrated together or alone for 8 weeks.	the levels of p53 in pancreas tissue of diabetics were markedly high. exercise and have anti-apoptotic effects on type 2 diabetic rats. crocin could decrease the blood glucose, p53 expression, and HbA1c levels in the diabetic-crocin group.	Ghorbanzadeh et al[52]

(Continued)

Table 1. (Continued)

IN VITRO/ANIMAL TRIALS/DOSAGE	RESULTS	REFERENCES
The rats were separated into three groups and remedied with CR and Met for 8 weeks. as such given 100 mg/kg of Met was dissolved in the physiological saline once per day for the whole of the test.	In the CR group the levels of insulin serum, HDL, cholesterol (which are also indicators of hypoglycemic functions), and pyruvate kinase increased.	Qiu et al[53]
Wistar rats were divided into control, type-1 diabetes induction, negative controls. Crocin dispensed for 4 weeks daily basis. and the prosperous induction of diabetes confirmed 14 days after STZ Prescription.	Diabetes disrupts the balance of oxidation-antioxidation, while crocin improved the antioxidant situation in the liver by affecting SOD1 gene expression and restitution of SOD and TAC levels.	Margaritis et al[54]
Fertilized embryos of zebrafish accumulated at 3 HPF and treated with CRC. The total level of embryo glucose was measured at 48 h post-treatment.	Crocin can increase the expression of insulin, phosphoenolpyruvate, and carboxykinase (a key gene involved with glucose metabolism). and reduces the level of zebrafish embryo glucose.	Kakouri et al[55]
Male Wistar rats were separated randomly into the following groups: normal, normal-treated, diabetic, and diabetic-treated groups. Diabetes received a single dose of STZ. every day the treated groups received crocin for 8 weeks.	Crocin Strengthened the anti-oxidant defense system by enhancing the effect of both SOD and catalase and recover OS by reducing MDA manufacture in pancreatic cells. Uncontrolled hyperglycemia did not change the GLT amount in non-treated rats and decreased the level of nitrate markedly.	Yaribeygi et al[56]
the type-2 diabetes model created by low-dose STZ into rats fed with the HFD. The treatment groups received a daily crocin for 6 weeks.	crocin could be effective in creating hyperleptinemia, hyperinsulinemia, insulin resistance, and weight gain. Also, the oxidative stress, which is enhanced due to the progress of diabetes reduced in the crocin treatment group.	Hazman et al[57]
Wistar albino rats were randomly divided into 5 groups to find diabetic Encephalopathy (one of the serious complications in diabetic patients) in STZ Induced Experimental Diabetes Mellitus.	findings showed that saffron extraction decreased the risk of hyperglycemia and hyperlipidemia and also reduce the oxidative stress in diabetic encephalopathy rats.	Samarghandian et al[58]
The rats were divided into 3 groups: saffron group, physiologic serum group, and the normal group. Daily injection of hydromethanolic extract of saffron was performed for 2 weeks.	the level of insulin in the test group markedly was enhanced and serum glucose markedly reduced. These results indicate that saffron extract has hypolipidemic and hypoglycemic effects on wholesome rats.	Arasteh et al[5]
Rats were separated into 6 groups of 10 animals: Control (C) Group, Sham + Streptozotocin (STZ) Group, Pinealectomy (PX) Group, PX + STZ Group, PX + Crocin (PX + Cr) Group, PX + STZ + Cr Group. Daily crocin treatment intraperitoneally for 15 days (50 mg/kg)	crocin significantly reduced serum BUN and Cr levels in the PX + STZ + Cr group. crocin treatment improved DN progression in addition to impaired histopathological, biochemical, immunohistochemical and parameters. It reduced TGF-β1 and suppressed oxidative stress.	Keelo et al[59]
40 diabetic Sprague Dawley male mice were selected with an average age of 4 weeks. Rats were divided into 5 groups including control, normal, damask rose petal, saffron petal, and saffron with damask rose petal groups. The study lasted 9 weeks, during which time 3 ml of herbal tea was given to rats by oral gavage.	In the saffron petal group, decreased TG, HBA1C, and IGF-1 were observed. Also, FBS, HDL, and LDL were decreased compared to the control group.	Majidi et al[60]

Some studies reported some beneficial effects of saffron on the cardiovascular system and myocardial tissue. According to these findings, saffron consumption alone can have protective effects on the myocardium. In type 2 diabetic men, saffron extract consumption and aerobic exercise can reduce the Troponin T and Heart-Type Fatty Acid Binding Protein (HFABP) levels.[76] However, consumption of saffron and other herbs like cardamom, cinnamon, and ginger as herbal treatments has no significant effect on endothelial function and BP (blood pressure), as risk factors for cardiovascular diseases.[7] Various articles researched the effects of saffron extract on metabolic factors, glycemic control, lipid profile, oxidative stress, and inflammation. For example, Milajerdi et al conducted a study that indicates that saffron hydroalcoholic extract may improve hyperglycemia control by decreasing FBS in T2DM patients.[73] In another study, Barari et al attempted to investigate the effect of saffron extract and aerobic training on serum hemoglobin A1c (HbA1c) and Apolipoprotein A-1 (Apo-A1) in men with type 2 diabetes mellitus. The results from this study showed that consumption of saffron extract regardless of aerobic exercise can increase the level of Apo A-1 in T2DM patients, which is valuable because lower levels of serum Apo A-1 are reported in diabetic patients with dyslipoproteinemia and cardiovascular diseases like cardiovascular autonomic neuropathy (CAN).[72,77] However, it does not affect the HbA1c level.[78]

Other studies attempted to investigate the effect of the saffron extract on oxidative stress. Azimi et al revealed that consumption of saffron, cinnamon, cardamom, and ginger as herbal remedies have significant effects on levels of oxidative stress markers and inflammatory factors in type 2 diabetic patients.[7] Also, Barari et al reported that saffron extract and aerobic exercise seem to be able to decrease and increase the levels of MDA and erythrocyte glutathione peroxidase (GPX) activity in men with type 2 diabetes, respectively.[79] Another study presented by Azimi et al showed that saffron extract and other herbal medicines have beneficial effects on cholesterol levels but not on measures of glycemic control, oxidative stress, and inflammation.[7] Newer evidence shows that the overproduction of pro-inflammatory cytokines plays a role in the formation of diabetes issues. Certain herbals, namely Saffron can help patients with diabetes to maintain inflammation and improve the hyperglycemic states.[80] Sepahi et al attempt to measure the effects of the saffron supplementation on inflammatory markers and fasting glucose levels in T2DM patients and evaluate the effects of crocin intake on reducing inflammation in patients with diabetic maculopathy. They found that saffron supplementation significantly decreased Fasting blood glucose (FBG) levels within 8 weeks in the patients who received saffron. Also, the expressions of TNF-α and its serum level beside the level of IL-6 mRNA were noticeably Downregulated.[81]

Lung volume loss, airway obstruction, airflow limitation, and also hypertension are risk factors for mortality in patients with type 2 diabetes. Rajabi et al performed a study to illustrate the effect of saffron supplementation and aerobic training on Blood pressure disparities, pulmonary function, and spirometric indices in women who are obese and overweight and are suffering from type 2 diabetes. Among these participants, this study shows that saffron consumption with exercise led to a significant decrease in blood pressure and improvement in pulmonary volume and capacities.[82]

Saffron and its extract can cause a noticeable reduction in plasma glucose levels according to experimental models. Moravej Aleali et al determine the effects of the saffron extract on the fasting plasma glucose (FPG), HbA1c, lipid profile, liver, and renal function tests in patients with type 2 diabetes. In the following double blind randomized clinical test, patients with type 2 debates who were on oral antidiabetic drugs were received saffron capsules or placebo and analyzed. These variables were measured before and after intervention after 3 months. At end of follow-up duration, in the saffron group, FPG, Cholesterol, LDL c, and LDL/HDL ratio against HbA1c, HDLC, API, and TG showed significant reduction compared to the control group ($P < .0001$). The results of this study indicate that saffron consumption can improve hyperglycemia and lipid profile in type 2 diabetic patients.[83]

In a randomized clinical trial, Karimi-Nazari et al investigated the effects of saffron on the lipid profile, glycemic and antioxidant status in individuals who are obese and overweight and who have prediabetes. The results of this study showed a noticeable effect of saffron supplementation on FBS, HbA1c, and DPPH (diphenyl-picryl-hydroxyl) levels.[84] In adjusting models, there was a marginal reduction in FBS and HbA1c in the saffron group in comparison to the placebo group. Furthermore, saffron supplementation tended to increase the DPPH radical scavenging activity and according to data of Sepahi et al, administration of crocin can affect central macular thickness (CMT) and improve best-corrected visual acuity (BCVA). The main purpose of this investigation is to examine the effects of saffron intake as an adjunct therapy to DM.[81] To investigate the effects of saffron supplementation on inflammation and metabolic responses in type 2 DM patients a double-blinded randomized control-placebo trial was conducted by Ebrahimi et al. The results of this study showed that saffron supplementation Compared to placebo caused a significant decrease in waist circumference and MDA However, saffron did not influence on other evaluated cardiometabolic risk markers in diabetic patients. In another study, they observed that *C. sativus* intake can result in a noticeable reduction of SBP (systolic blood pressure).[85,86]

In a study, Aghajani et al investigated the effect of aerobic and resistance training in 8 weeks with the aqueous extraction of saffron on malondialdehyde and glutathione peroxidase among T2DM. In this clinical trial, participants were divided into 6 groups: placebo, aerobic training, aerobic training with supplement consumption, resistance training, and resistance training with supplement consumption. The results concluded that the Level of malondialdehyde was significantly lowered in placebo and aerobic training with supplement before intervention. The level of glutathione peroxidase was noticeably increased in aerobic training with the supplement, resistance training, and resistance training with supplement groups after intervention. This study demonstrates that Aerobic and resistance training and their combination with saffron consumption can be considered an effective method to improve the peroxidase and antioxidant balance.[87] Hooshmand Moghadam et al studied the effect of saffron supplementation and exercise in men with type 2 diabetes. In all groups except the control group, insulin, FBG, IL-6, IL-1β, HOMA-IR, HbA1c, TNF-α, were decreased significantly. IL-10 was increased in 3 groups. A positive correlation was observed between the concentration changes of BFP and TNF-α, IL-10, IL-6, and IL-1β in the 3 intervention groups. It was also concluded that simultaneous consumption of saffron supplement and exercise could be of high efficacy. Specially in terms of anti-inflammatory effects.[88] Furthermore, in a critical appraisal of literature Kadoglou et al stated that the included clinical trials mostly showed weak effects of saffron and its main constituents on cardiovascular risk factors including modest lowering of FBG, without a significant reduction of HbA1c in type 2 DM patients, moderate or controversial hypolipidemic effect, negligible hypotensive effects, as well as inconsistent modification of the parameters of metabolic syndrome.[89]

Table 2 summarizes the main findings of the clinical trials on the anti-diabetic potential of saffron.

Conclusion

In summary, findings from this review highlight the effects of saffron and its chief ingredients including crocin on various parameters of diabetes and its complications. Several in vitro, in vivo, and clinical trial studies were reviewed. Clinical trials

Table 2. Clinical trials on the anti-diabetic potential of saffron.

HUMAN TRIAL/DOSAGE	RESULTS	REFERENCE
204 T2DM patients; 4 groups used 3 black tea glasses as well as either 3g cardamom, cinnamon, ginger, or 1g of saffron. 1 control group consumed only 3 tea glasses without any herbal medicine for 8weeks.	After an 8-week intervention, cinnamon, cardamom, ginger, and saffron usage had noticeable effects on total cholesterol, LDL, and HDL levels in comparison to controls. The herbal remedies inspected had noticeably useful effects on cholesterol, but not on levels of glycemic control, oxidative stress, and inflammation.	Azimi et al[7]
204 T2DM patients; 4 intervention groups taking 3g cinnamon, 3g cardamom, 1g saffron, or 3g ginger with 3 black tea glasses, and 1 control group taking only 3 tea glasses without any herbals, within 8weeks.	Giving the herbal drugs as complementary remedies could influence BP and sICAM-1 condensations but there was no noticeable variation among the plants in terms of affecting anthropometric levels, BP, and endothelial role.	Azimi et al[90]
24 men with T2D, divided into 4 groups (1. control, 2. saffron juice, 3. aerobic exercise, 4. aerobic exercise and saffron juice). Saffron juice was applied in a measure of 3mg/kg/BW per daily. Aerobic exercise, 3days a week, within 8weeks, accompanied by 55%-70% of utmost HR was done.	Aerobic practice, saffron juice, and saffron combined with Aerobic practice was no noticeable decrease in HbA1c levels in diabetics. However, in all 3 groups, a noticeable decrease in Apo A-1 levels was noticed.	Barari et al[78]
24 T2DM men in 4 groups (1. control, 2. saffron juice, 3. aerobic practices, 4. combination of aerobic practices and saffron juice). Saffron juice with 100mg/day was taken. Aerobic practices 3days in a week within 8week with 55%-70% of utmost HR were executed.	Saffron usage may usefully support the myocardium from harm. A combination of saffron juice and aerobic practices can reduce Troponin T and HFABP levels in men with T2DM.	Barari et al[76]
24 men with T2DM in 4 groups (1. saffron juice, aerobic exercising, aerobic exercising + saffron juice, and control groups.) The saffron juice was taken at a 3mg/kg dose. The aerobic practice was done 3days a week, within 8week, at 55%-70% of utmost HR.	Antioxidant saffron compounds are beneficial in the diminution and tissue damages inhibition after physical performances. Aerobic exercising + saffron juice can reduce MDA and also increase erythrocyte GPX function levels in T2 diabetics.	Barari et al[79]
Study groups; 1) Control group: not using complements or exercise within the study 2) placebo group 3) Aerobic practice 4) Aerobic practice + saffron complement consumption for the rate of 3mg/kg of body weight. 5) Resistance training 6) Resistance training + saffron complement consumption for the rate of 3mg/kg of body weight. The aerobic group training schedule contained 8week + 3 sessions per week. 36 men with T2DM (with a history of a minimum of 3years), serum glucose levels higher than 120mg/dl and not exercising regularly for a minimum in the last 6month were included. All groups took serum glucose-lowering drugs (glibenclamide and metformin) + blood lipid-lowering drugs (atorvastatin) + blood pressure-lowering drugs (losartan). Saffron powder t.i.d. in solution for 8weeks.	Aerobic and resistance training + saffron consumption are noticed as a practical method for enhancing the peroxidase and antioxidant equivalence. This study showed that aerobic practice and regular resistance + saffron complementation can be more useful in enhancing peroxidant and antioxidant equivalence in T2DM people and prevent oxidative stress posed by practice and diabetes. This kind of practice and complementation can be used as an effective way to correct peroxidant equivalence. Also in T2D Taking other training ways particularly simultaneous training is beneficial.	Aghajani et al[87]
50 patients with DM in Zabol; randomly divided into 2 intervention groups and control. The intervention group took 300mg saffron capsules; while, the control group was taken placebo capsules. The capsules were used daily between 12 and 2 p.m. for 1week. The patients' anxiety amounts were reinspected after a week. The amounts of anxiety were evaluated by Spielberger's Anxiety questionnaire.	This study showed the saffron oral capsules were useful in lowering anxiety in diabetic patients. Saffron has been proved to have antispasmodic, relieving, carminative, and appetite trigger results which is helpful in the prevention and treatment of many diseases. Saffron can be helpful in anxiety management in diabetic and other patients.	Dehghanmehr et al[74]
80 T2D patients were divided into *Crocus sativus* and placebo groups and used *C. sativus* or placebo within 12week respectively. At the end of the 12-week intervention, the variations between the 2 groups were evaluated. In this study, there had not been any noticeable changes in dietary usage and physical activity between the 2 groups.	*C. sativus* complementation in comparison to the placebo caused a noticeable reduction of SBP. This study showed that daily complementation together with 100mg *C. sativus* powder can correct SBP. Although, it did not noticeably improve DBP, nephropathy indexes, and liver functions in T2D patients after 12week of performance.	Ebrahimi et al[85]

(Continued)

Table 2. (Continued)

HUMAN TRIAL/DOSAGE	RESULTS	REFERENCE
80 T2D patients with an average age of 54 years; randomly divided equally into 2 groups to use either saffron pills (100 mg/day) or placebo within 12 weeks. In this study, the fasting blood samples were taken at first and after the intervention, term to quantify glycemic features, lipid profile, inflammation, and oxidative stress biomarkers. Anthropometric indexes and dietary usage were evaluated at the first and end of the study.	In comparison to the placebo, saffron complementation caused considerable decreases in MDA and waist circumference. considerable differences in other indexes (anthropometric parameters, FBG, serum insulin, HbA1c, insulin sensitivity indexes, lipid profile, TAC, high-sensitivity C-reactive protein, and TNF-α) were not found statistically among the study groups. 12 weeks of saffron complementation had useful effects on serum MDA amounts as well as waist circumference in diabetic patients. Although, saffron did not influence other evaluated cardiometabolic venture markers in diabetics.	Karimi et al[86]
75 prediabetic patients (36 in the cure and 39 in the placebo groups) randomly divided to take saffron (15 mg/d) pills or placebo within 8 weeks. Serum amounts of lipid profile, FBS, HbA1c, BUN, creatinine, and DPPH radical scavenging acting were evaluated biochemically at first and 8 weeks after cure.	Within-group comparisons showed a considerable effect of saffron complementation on FBS, HbA1c, and DPPH amounts. However, there had not been any considerable changes in anthropometric actions, lipid profile, and renal markers after saffron usage in comparison to placebo. Saffron complementation can improve glycemic and antioxidant indexes in overweight/obese prediabetic individuals but it has no useful effect on lipid profile and anthropometric parameters.	Karimi-Nazari et al[84]
54 T2D patients randomly got either saffron or placebo b.i.d other than routine antidiabetic cures within 8 weeks. Serum condensation of FBS, 2-h plasma glucose, HbA1c, total cholesterol, TG, high-density lipoprotein, and low-density lipoprotein were evaluated as the metabolic control markers. Anthropometric amounts and BP were also evaluated at first, every 2 weeks within the intervention and the end of the study.	The base metabolic parameters were similar in the 2 groups. FBS serum amount considerably decreased within 8 weeks in the saffron group in comparison to the placebo. Other metabolic parameters like serum lipids, BP, and HbA1c were similar. Saffron hydroalcoholic extract may back up blood glucose control via decreasing FBS in T2D patients. Although, the saffron extract has no noticeable effect on other sides of diabetic regulation among diabetic patients.	Milajerdi et al[73]
60 T2DM patients were divided randomly and equally into 2 groups as saffron and placebo to taking 100 mg/day powder of saffron or starch capsules (1 capsule) during a term of 8 weeks. Fasting blood was sampled at the base and the end of the intervention. FBG was instantly analyzed via the auto-analyzer. The serum amount of IL-6, TNF-α, and IL-10 were evaluated by ELISA measure with laboratory kits. Moreover, RT-PCR evaluated the expression amount of TNF-α, IL-6, and IL-10 based on the mRNA amount.	Saffron complementation noticeably decreased the FBG and the serum amount of TNF-α within 8 weeks in comparison to placebo. Moreover, saffron complementation noticeably down-regulated the gene expression of TNF-α and IL-6. This study indicated that saffron adjusts glucose and inflammation status amounts in T2DM patients by decreasing the amounts of several inflammatory mediators.	Mobasseri et al[80]
64 T2D Participants used either 15 mg of saffron or placebo capsules (2 pills a day) within 3 months. After 3 months anthropometric indexes, dietary usage, FPG, HbA1c, lipid profiles, liver enzymes, and renal function tests were evaluated before and after the intervention.	After the 3 months intervention, In the saffron group, FPG, HbA1c, cholesterol, LDL c, and LDL/HDL proportion decreased noticeably in comparison to base.	Moravej Aleali et al[83]
48 T2D obese/overweight women were non randomly divided into 4 equal groups including placebo, training + placebo, saffron + placebo, and saffron + training. The saffron group + training and training + placebo groups performed aerobic training with a severity of 60%-75% of maximum HR within 8 week (3 sessions in each week). An everyday dose of 400 mg of saffron powder (once per day) was taken within 2 months.	In this study, saffron with practice resulted in a noticeable improvement in pulmonary bulk and capacities, as well as a decrease in BP in T2D obese/overweight women. In the 3 groups of exercise, saffron and training + saffron was seen a decrease in SBP and anthropometric indexes (weight, BMI, and body fat percent).	Rajabi et al[82]
64 T2DM patients; used either 15 mg of saffron or placebo capsules (2 pills in each day) within 3 months. Anthropometric indexes and homocysteine as well as serum anti-inflammatory and antioxidant parameters and dietary usage were evaluated before and after the intervention.	In this study homocysteine amounts, antioxidant state and inflammatory biomarkers did not improve among T2DM patients after taking saffron. After 3 months-cure, IL-6, and TNF-α raised considerably in the 2 groups. TAC, MDA, hs-CRP, and IL-10 did not change after the cure term. Homocysteine was reduced noticeably in the control group.	Shahbazian et al[91]

(Continued)

Table 2. (Continued)

HUMAN TRIAL/DOSAGE	RESULTS	REFERENCE
60 patients with resistance diabetic maculopathy to common therapy containing macular photocoagulation, intravitreal injecting of anti-vascular EGF agent (bevacizumab) together with or without steroid (triamcinolone) were examined in 3 groups. Patients in the crocin groups used 5 mg or 15 mg crocin pills each day within 3 months, while the placebo group used 1 placebo pill each day within the study.	This study showed taking a crocin 15 mg pill each day could noticeably reduce HbA1c, and CMT and improve BCVA in comparison to the placebo group. Although taking the crocin 5 mg pill each day could clinically improve HbA1c, FBS, CMT, and BCVA, there were not any notable differences in contrast to the placebo group. This study revealed the crocin impact as a powerful antioxidant and neuroprotective for resistance of DME treatment in a short period.	Sepahi et al[81]
70 adult volunteers among 30-60 years were joined in this double-blind, randomized, placebo controlled clinical trial. Participants were overweight-obese with body mass index (BMI) between 25 and 35 kg/m^2 and had type 2 diabetes for at least 6 months and intake 100 mg/day saffron powder for 8 weeks	these results indicate that saffron remarkably lessen hyperglycemia, liver enzymes (AST and ALT) levels and TG in patients with type 2 diabetes. depression, sleep quality, and quality of life also notably improved by Saffron.	Tajaddini et al[75]
60 obese men with DM were randomly divided to 4 groups (1. CT: Placebo + Concurrent Training (n = 15), 2. S: Saffron supplementation (n = 15), 3. CTS Concurrent Training + Saffron supplementation (n = 15), 4. CON: control (n = 15); This test lasted 12 weeks. The men in the CT group received a placebo and did exercise 3 times per week for 12 weeks the men in the S group daily received one pill of saffron supplementation containing 100 mg of saffron, the men in the CTS group did an exercise program with one pill of saffron supplementation containing 100 mg saffron.	In all groups except the control group, insulin, FBG, IL-6, IL-1β, HOMA-IR, HbA1c, and TNF-α, were decreased significantly. IL-10 levels were increased in three groups. A positive correlation was observed between the concentration changes of BFP and TNF-α, hs-CRP, IL-10, IL-6, and IL-1β in the three intervention groups And drastic changes were observed between the group of simultaneous consumption of saffron supplement and exercise.	Hooshmand Moghadam et al[88]

Abbreviations: ACC, adenoid cystic carcinoma; AGEP, advanced glycation end products; ALT, alanine transaminase; AMPK, activated protein kinase; AST, aspartate transaminase; BCVA, best-corrected visual acuity; b.i.d., twice a day; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CAT, catalase; CDA, comorbid depression; Cham, chamomile; CMT, central macular thickness; CR, Crocin_I; CRC, color remediation cartridges; CRP, C-reactive protein; DBP, diastolic blood pressure; DC, diabetic control; DM, diabetes mellitus; DME, diabetic macular edema; DPPH, diphenylpycrylhydrazyl; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; EGF, endothelial growth factor; FBG, fasting blood glucose; FBS, fasting blood sugar; FBS, fasting blood sugar; FPG, fasting plasma glucose; GLT1, glycemic levels test; GLUT4, glucose transporter type 4(protein); GPX, glutathione peroxidase; GSH, glutathione; HbA1c: hemoglobin A1c; HG-FFA, hyperemesis gravidarum-free fatty acid; HPF, hour post fertilization; HR, heart rate; HbA1c, hemoglobin A1c glycosylated hemoglobin; IVICAM-1, intercellular adhesion molecule-1; HFABP, heart-type fatty acid binding protein; hs-CRP, high sensitivity C-reactive protein; IL, interleukin; T2, Type 2; SWLS, satisfaction with life scale; ACE, angiotensin converting enzyme; ROS, reactive oxygen species, or AMPK or 5′ Adenosine Monophosphate-Activated Protein Kinase; MAD, malondialdehyde; MAP, mean arterial pressure; MAPKs, a mitogen-activated protein kinase; MDA, malondialdehyde; MWM, Morris water maze; MET, metformin; MTT, mean transit time; NF-KB, nuclear factor kappa B; PSQ I, Pittsburgh Sleep Quality Index; PAI-1, plasminogen activator inhibitor-1; PP, pulse pressure; P53, tumor Protein P53; PC12, *a* cell line derived from a pheochromocytoma of the rat adrenal medulla; PCK1, phosphoenolpyruvate carboxykinase 1; RT-PCR, real-time quantitative reverse transcription; Saf, saffron; SBP, systolic blood pressure; SOD1, superoxide dismutase 1; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; STZ, streptozotocin; SSE, saffron stigma extract; SOD, superoxide dismutase; TAC, total antioxidant capacity; TBARS, thiobarbituric acid reactive substance; t.i.d., three times per day; T2DM, type 2 diabetes mellitus; T2D, type 2 diabetes; TG, triglyceride; TNF-α: tumor necrosis factor-alpha; XO, xanthine oxidase.

revealed multiple positive effects of saffron on diabetic patients including improvement of metabolic factors, glycemic control, lipid profile, oxidative stress, and inflammation. Moreover, beneficial features of saffron components were detected in the cardiovascular system. Blood pressure state and pulmonary function, as well as depression, anxiety, sleep quality, and life satisfaction of diabetic patients. Furthermore, clinical trials and animal studies reported the synergistic effects of saffron consumption along with aerobic exercise. Saffron extracts improved diabetic status in STZ-induced diabetic rats via different mechanisms. Enhancement of antioxidant defense systems by boosting the enzymatic activities of SOD and CAT leads to decreased degrees of pancreatic dysfunction as well as kidney and liver injury in diabetic rats. The beneficial effects of saffron components on the metabolic condition of diabetic animals including hyperglycemia, dyslipidemia, and insulin resistance, were also confirmed in multiple studies. The suggested underlying mechanisms involved anti-oxidant, anti-inflammatory, and apoptosis regulatory potentials of saffron. In vitro studies confirmed the same anti-diabetic effects, using saffron components on different cells including PC12, microglial and skeletal muscle cells. Overall, the favorable effects of saffron are promising for the management of diabetes mellitus, although the possible risk of bias in the included studies should be considered. There is a need for further research with a solid design for revealing the underlying mechanism of these effects. Future clinical trials are needed to be conducted in populations with greater homogeneity and consistent regiments of saffron to reach a more detailed conclusion about the optimal dosage for treatment of diabetic patients.

Author Contributions

Study concept and design: ND. Acquisition of data: AS, AT, SSS, RK. Drafting of the Manuscript: AS, AT, SSS, RK, HT, MT, NSE, SmmAd. Critical revision of the manuscript for important intellectual content: ND, RK. Study supervision: ND.

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