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Meta-analysis

The potential role of saffron (Crocus Sativus L.) and its components in oxidative stress in diabetes mellitus: A systematic review

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SUMMARY

Background and aims: Diabetes mellitus is one of the most important life-threatening metabolic diseases of the 21st century. The use of complementary and alternative medicine in diabetic patients seems to be increasing. Saffron, a valuable herbal medicine, has several pharmacological properties such as antioxidant effect, which can play important role in ameliorating the complications of diabetes. The aim of this study was to systematically review the therapeutic effects of saffron and its bioactive components on oxidative stress in diabetes mellitus.

Methods: In this systematic review, databases such as PubMed, SCOPUS, Embase, ProQuest, and Web of Sciences were searched from the beginning to December 2021. All eligible *in vitro*, animal, and human studies that examined the effect of saffron on oxidative stress indices in diabetes were prepared in the form of a full article in English.

Results: In the end, only 31of the 389 articles met the criteria for analysis. Of the 31 articles, 4 were in-vitro studies, 25 were animal studies, and 2 were clinical trials studies. Saffron supplementation may activate insulin receptor substrate 1 (IRS1) and peroxisome proliferator-activated receptor gamma (PPAR-γ), which can improve hyperglycemia and insulin transduction signal in adipose tissue, and regulate glucose metabolism, leading to an increased nuclear factor erythroid 2–related factor 2 (Nrf2), HO-1 expression, amelioration of mitochondrial function, and an increased levels of antioxidant enzymes.

Conclusion: Most studies have shown that saffron supplementation significantly enhanced the production and activity of antioxidant enzymes and decreased oxidative stress indices in diabetes mellitus. However, human pharmacokinetic and more accurate clinical trial studies are needed to determine dose ranges and the exact mechanisms of action of saffron and its active components in diabetes.

1. Introduction

Diabetes is one of the most common metabolic diseases, which threatens human health in the 21st century. The number of diabetic patients is dramatically increasing worldwide [1, 2]. The global prevalence of the disease in 2015 was 8.8% (415 million) of the world's population, and it is estimated that the prevalence of diabetes in 2030 and 2040 will increase to about 440 and 642 million people in the world, respectively [3, 4]. Different types of diabetes occur due to complex interactions between environmental factors, genetic factors, and lifestyle [5, 6]. Diabetes mellitus (DM), defined as an abnormal increase in blood sugar (hyperglycemia), is caused by a deficiency in insulin secretion, insulin resistance, or a disorder in the metabolism of fats, proteins, and carbohydrates [7–9]. Chronic hyperglycemia can cause microvascular complications, such as retinopathy, neuropathy, nephropathy, and macrovascular complications including cerebrovascular and coronary artery disease [10, 11]. Hyperglycemia increases oxidative stress and production of free radicals that play the main role in the pathogenesis of diabetes complications [10, 12, 13]. The overproduction of reactive oxygen species (ROS) is mainly due to decrease in generation of endogenous antioxidants including

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glutathione peroxidase (GSH–Px), superoxide dismutase (SOD) and catalase (CAT) [14]. Moreover, various organs such as pancreas are prone to oxidative stress damage, even when the level of antioxidant enzymes is slightly reduced [15].Diabetes treatment options include medications and lifestyle modifications such as physical activity and nutrition [16, 17]. Therefore, today, complementary therapy and alternative medicine especially herbal remedies are increasingly used in chronic diseases like diabetes mellitus [18, 19]. Saffron is a spice derived from *Crocus Sativus* L., and due to its special color, smell and taste, it is widely used to prepare cosmetics and food [20, 21]. Saffron also contains more than 100 bioactive components including safranal, crocin, and crocetin [20].

2. Chemical composition of stigma

Saffron is the dried red stigma and attached yellowish style [28]. Saffron is characterized by its peculiar features including aromatic smell, bitter taste, and intense red color [29]. Its bitter taste originates from picrocrocin, α β-D-glucoside of hydroxyl-safranal [30]. This bitter flavored substance can be crystallized and produces glucose and aldehyde safranal by hydrolysis [30]. The chief components of stigma are crocetin, its glucosidic derivatives, safranal, picrocrocin, crocins and flavonoids including kaempferol and quercetin [31].

2.1. Crocin

Crocin is 8,8-diapocarotene-8,8-dioic acid and has the chemical formula of C44H70O28 [32]. Crocin is one of the main pigments of saffron (80% of saffron), which is responsible for the golden bright-yellow-red color of saffron [33]. In addition, most other carotenoids are not water-soluble [33]. Therefore, crocin is a special carotenoid that is mostly used as a dye in food and medicine. Contrary to saffranal, crocins (digentiobiosidecrocetinor crocin-1 or a-crocin, tricrocin or crocin-2, crocin-3 or gentio glucoside crocetin, glucoside crocetin or crocin-4, diglucoside crocetin or crocin-5) are permanent under ambient conditions [33, 34].

2.2. Crocetin

Crocetin (8, 80-diapo-8, 80-carotenoic acid) is a carotenoid with a unique lipophilic property that has the structure of polyunsaturated conjugated olefin acid [35].Crocetins (crocetin I or a-crocetin, b-crocetin, crocetin II, g-crocetin) in saffron are derived from oxidative degradation of zeaxanthin precursor.

2.3. Picrocrocin

Picrocrocin with the chemical formula of C16H26O7 is a precursor of saffron aroma components (4-hydroxy-2,6,6-trimethyl-1-cyclohexen-1- carboxaldehyde) and colorless monoterpene glycoside.Picrocrocin is the second most abundant substance (approximately 13.1% of saffron dry matter), which is responsible for the bitter taste of saffron [36, 37].

2.4. Saffranal

Saffranal (2,6,6-trimethyl-1,3-cyclohexadiene-1-carboxaldehyde), an aglycon of picrocrocin and monoterpene aldehyde with a molecular weight of 150. 21 g/mol, produces saffron's aroma and is the essential component of the saffron's distilled important oil [38]. It is believed that safranal is a degradation product of the carotenoid zeaxanthin via the intermediate picrocrocin [39]. In addition, saffron has anti-hypertensive, anti-ischemic,hypolipidemic, anti-tumor, antidepressant, anti-convulsant, anti-inflammatory, and antioxidant properties [23, 24]. Although several studies [25–27] have evaluated the effect of saffron on pathways and indicators of oxidative stress in diabetes,but so far, no systematic review study has been conducted to investigate the effects of saffron on oxidative stress pathways. The purpose of this systematic review is to summarize and compare the results of studies on the role of saffron in oxidative stress indices in diabetes.

3. Method

This systematic review was conducted using the Guideline of Preferred Reporting Items Systematic Meta-Analyses Checklist (PRISMA) [40]. All articles were transferred to Endnote software at the beginning of this systematic review and duplicate articles were eliminated.

3.1. Search strategy

The online searches of databases including PubMed, SCOPUS, Embase, ProQuest, and sciences direct were conducted by two independent authors without a time limit until the end of December 2021. The keywords used in the mentioned databases were as follows: saffron" [Mesh] or "crocetin" [Mesh] or "safranal" [Mesh] or "crocin" [Mesh] or ""Crocus sativus" [Mesh] or"crocetin supplementation" [tiab] or "saffron supplementation" [tiab] or "safranal supplementation" [tiab] or "crocin supplementation" [tiab] or "Crocus sativus supplementation" [tiab] and "diabetes mellitus" [Mesh] or "diabetes" [Mesh] or type 2 diabetes" [Mesh] or "type II diabetes" [tiab] or ""T2DM" [tiab] or "non-insulin-dependent diabetes mellitus" [tiab] or "NIDDM" [tiab] "type 1 diabetes" [Mesh] or "type I diabetes" [tiab] or "T1DM" [tiab] or "insulin-dependent diabetes mellitus" [tiab] or "IDDM" [tiab] or "gestational diabetes mellitus" [tiab] or "B-cell function " [tiab] or "impaired glucose tolerance" [Mesh] or "glycemic outcomes" [tiab] or "fasting blood sugar" [tiab] or "impaired fasting glycaemia" [Mesh]or "glucose intolerant" [tiab] or "glucose intolerance" [tiab]"HOMA-IR" [tiab] or"fasting blood glucose" [tiab] or "insulin secretion" [tiab] or "glucose tolerance" [tiab] or "glucose tolerant" [tiab] or "high glucose" [tiab] or "insulin-resistant" [tiab] and "oxidative stress" [Mesh] or "oxidative phosphorylation" [Mesh] or "Malondialdehyde" [tiab] or "total antioxidant capacity" [tiab] or "total antioxidant status" [tiab] or "Glutathione peroxidase" [tiab] or "Superoxide dismutase" [tiab].

3.2. Eligibility criteria

The inclusion criteria in this study were as follows: (a) Human, animal, and invitro studies, (b) the intervention was saffron supplementation, (c) saffron should be used for treatment alone and not in combination with other compounds, and (d) the outcome was the effect of saffron on oxidative stress.

3.3. Exclusion criteria

In this systematic review, we excluded studies that: (1) the intervention is not relevant to saffron is supplemented with other compounds (2) saffron has been used as a treatment for other diseases, (2) books' chapters, editorial, commentary papers, report, presentation, and review, (3) articles in a language other than English.

3.4. Data extraction

Two authors (A.K. and A.M.) evaluated the titles and abstracts of the selected articles based on the inclusion criteria and screened

them for data extraction. In the next stage, eligible studies were evaluated based on the authors' names, topic of study, saffron supplement dose, duration of supplement use, and main conclusion. The third researcher (R.N.D.) evaluated the accuracy and quality of the extracted information.

3.5. Risk of bias assessment

The risk of bias was assessed by two authors (A.K. and R.N.D) for human, animal, and *in vitro* studies. The overall degree of bias in randomized controlled trials was evaluated using the Cochrane risk of bias (ROB) [41]. The SYRCLE risk of bias tool was applied to measure the overall risk of bias in animal studies [42]. Also, the quality of the *in vitro* studies was assessed using the OHAT risk of bias tool [43]. These tools have seven domains including allocation concealment, random sequence generation, performance bias, attrition bias, reporting bias, detection bias, and other bias sources. Based on any methodological defect that might affect the findings, each domain was ascribed a "high risk" score. A "low risk" score was assigned to each domain if there was no defect for that domain. If the information was not sufficient to determine the effect, it would get an "unclear risk" score. If this test is "low-risk" for all domains, the study has a high-quality, completely low-risk study.

4. Results

4.1. Selected articles

The study flowchart is presented in Fig. 1. A total of 389 articles were selected from databases, such as Embase, PubMed, Scopus, ProQuest, and Web of Sciences. Two hundred and twenty-six articles were duplicates, all of which were removed, and 163 articles remained. Of these, 51 articles were excluded from the study due to lack of inclusion criteria, 38 reviews, eight conference abstracts, one book chapter, three letters, one editorial, and 81 non-related studies were found. Finally, 31 eligible articles were included in this systematic review. A summary of the studies are shown in Table 1.

4.2. Findings from the quality assessments

The results of the methodological quality assessment of included human, animal, and *in vitro* studies are presented in Figs. 2–4. The results of the blinded outcome assessment for human studies showed that one study was classified as an unclear risk of bias (Fig. 2). The SYRCLE risk of bias tool was used to evaluate the quality of animal studies. The baseline characteristics exhibited that most of the studies were rated as low risk of bias for the group similarities at sequence generation, selective outcome reporting, and other bias category sources. In most of these studies, randomization in animal housing, blinding outcome assessment and random outcome assessment were not mentioned clearly. Methods of blinding were properly described in 20% of the included studies. Moreover, the risk of incomplete outcome data was identified in 85% of the studies and the risk of allocation concealment was identified in 70% of the animal studies (Fig. 3). The OHAT risk of bias tool was used to evaluate the *in vitro* studies.

The qualitative assessment represented that most studies were appraised as low risk of bias for the similarities at experimental conditions across groups, sufficient administration of dose or exposure level, confidence in the exposure characterization, full report of outcome, and the other potential threats to internal validity.

In all of these studies blindness of assessors were not pointed clearly. Adequate allocation of groups was properly mentioned in 66% of the included studies. Complete report of outcome was high risk in one study (33%) (Fig. 4).

4.2.1. Invitro studies

The characteristics of all the in-vitro studies reviewed in this systematic review are shown in Table 1. In these studies, the dose of saffron supplement used varied from 0.1 μM/ml to50 μM/ml [44–47].

4.2.2. Animal studies

The characteristics of all in vivo studies included in this systematic review are shown in Table 1. Of the 26 animal studies, 25studies were conducted in rats, and one was in mice. Also, in four out of 26studies, animal models had type1diabetes [48–51], and in the remaining 21 cases, the animal model had type 2 diabetes [25–27, 52–69]. In these studies, the dose of saffron supplementation varied from 0.025 mg/kg/day to 200 mg/kg/day. Also, the duration of intervention on animals was different from 21 days to 8 weeks.

4.2.3. Human studies

The characteristics of the two human studies included in this study are shown in Table 2. All studies were on both genders. Also, the sample size of clinical trials varied from 90 to 204 participants with an average age of 20–66 years. In addition, the period of the supplementation varied between 8 and 12 weeks, and the dose of saffron supplements varied from 100 mg/day per day to 1 g/day in clinical trials. All of the studies also used a parallel design [20, 70].

4.3. Findings from the in-vitro studies

Yang, Huo et al. [44], have investigated the effects of crocin on oxidative stress of microglial cells related to the diabetic. The authors reported that crocin Could improve vision loss, neuronal damage, and other diabetic retinopathy-induced complications by reducing ROS and iNOS production, and also suppressing of phosphatidylinositol 3-kinase (*PI3K*)/protein kinase B (*AKT*) pathways. Suh, Chon et al. [45], found that the amount of 5 μM up to 20 μM of saffron could significantly decrease oxidative stress indices and attenuated methylglyoxal in RAW264.7 cells. In another study, Mousavi, Tayarani et al. [46], have investigated the effect of crocin and saffron extracts on ROS-induced high glucose toxicity in PC12 cells. They have reported that treatment with crocin and saffron extract decreased ROS and increased GSH in these cell lines. Li, Liu et al. [47], showed that the amount of 0.1, 0.5 and 1 μM of crocin could significantly decrease ROS production and increase SOD in RAW264.7 cells.

4.4. Findings from the animal studies

4.4.1. The effect of saffron on oxidative stress indices in animal models of diabetes mellitus

Samarghandian, Azimi-Nezhad et al. [26], Showed that intraperitoneal administration of saffron in different dosages (10, 20, and 40 mg/kg) for 4 weeks considerably decreased lipid peroxidation level (MDA)and nitric oxide (NO) in type 2 diabetic rats. In another study carried out by Rahbani, Mohajeri et al. [52]they observed a considerable reduction in MDA level after receiving 40 mg/kg I.P, saffron for eight weeks. In a study conducted by Abou-Hany, Atef et al. [50]in 2010 on type 1 diabetic rats, they concluded that supplementation with 20 mg/kg, orally of saffron for eight weeks could reduce oxidative stress index levels such as MDA. Moreover Qiu, Jiang et al. [27] have shown that 50 mg/kg/day of saffron supplementation for eight weeks decreased ROS and MDA. Also, other study by Bahmani, Bathaie

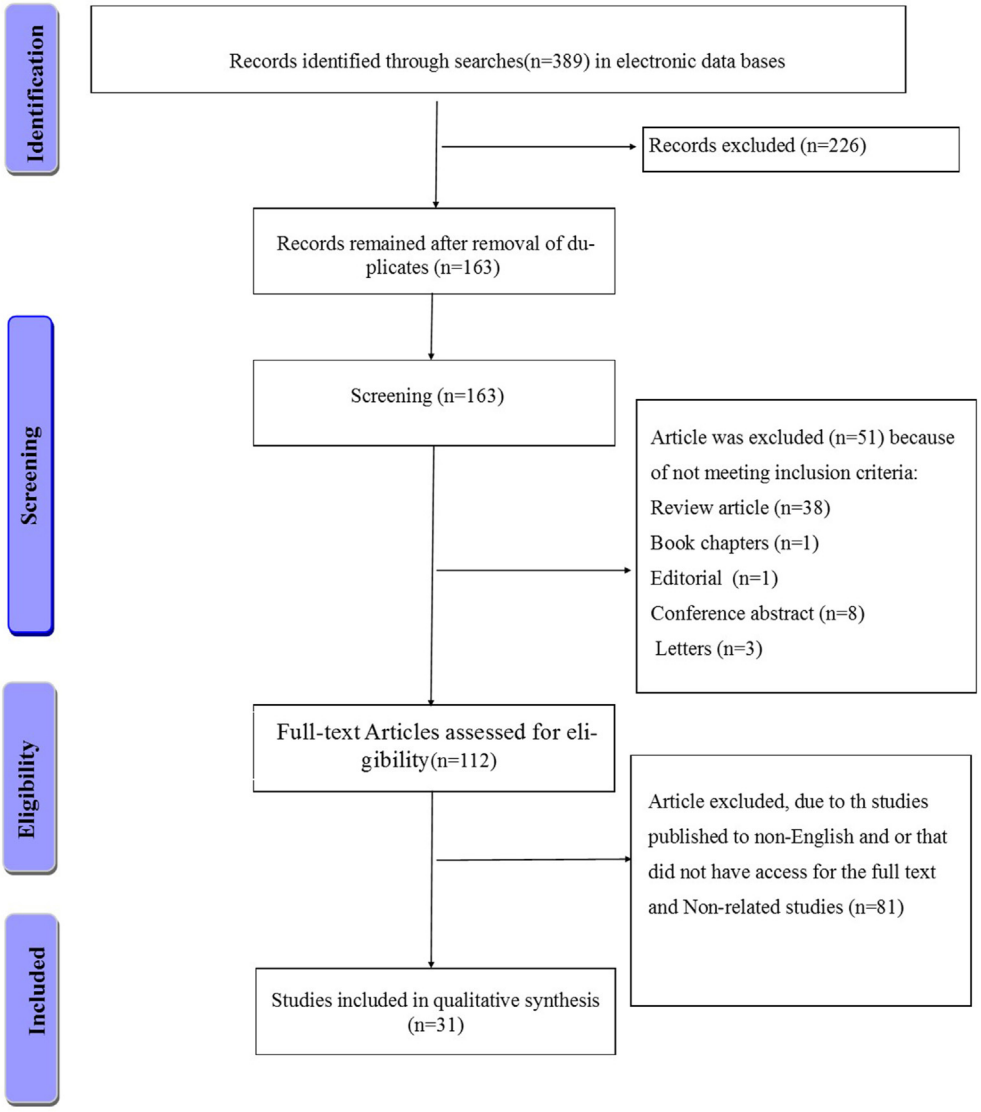

Fig. 1. Flowchart of the process for selecting studies for the systematic review.

et al. [56]indicated that the oral administration of 100 mg/kg/ saffron for 8 weeks significantly decreased lipid-peroxidation level (MDA) and NO in diabetic rats. Motamedrad, Shokouhifar et al. [54]reported reduced levels of MDA, in diabetic rats following saffron supplementation (25 and 100 mg/kg orally) for 21 days. Animal studies showed a wide range of saffron doses could be well tolerated by animals without exposure to toxicity. Overall, the findings of animal studies suggest that saffron supplementation may play a potential role in reducing lipid peroxidation indices such as MDA, Thiobarbituric acid reactive substances (TBARS), and protein-carbonyl contents. Other studies have also shown the effect of saffron on diabetes, which are listed in Table 1.

4.4.2. The effect of saffron supplementation on antioxidant biomarkers in animal models of diabetes mellitus

Abou-Hany, Atef et al. [50] after administering 20 mg/kg saffron orally for eight weeks in type 1 diabetic rats, observed a remarkable enhancement in antioxidant enzymes like SOD and GSH. In another similar study, Hemmati, Zohoori et al. [25] showed that using saffron at the different dosages25 and 100 mg/kg orally for 21 days significantly increased TAC in experimental diabetic rats. In other study, Bahmani, Bathaie et al. [56] investigated the effects of saffron on oxidative stress markers in diabetic rats. Diabetic rats were orally treated with saffron at 100 mg/kg of body weight dose for eight weeks. Saffron treatment significantly increased anti-oxidant enzymes such as SOD, GSH, and CAT. Motamedrad, Shokouhifar et al. [54] showed that 25, and 100 mg/kg/day of oral saffron supplementation for 21 days enhanced TAC. Also Qiu, Jiang et al. [27] indicated that the expression of Nrf2 and oxygenase-1 (HO-1) increased in diabetic mice after administration of crocin (50 mg/kg/ day) for eight weeks. Moreover, Samarghandian, Azimi-Nezhad et al. [26]showed that the administration of 10, 20, and 40 mg/kg saffron (I.P) for four weeks significantly increased SOD, GSH, and CAT. The results of animal studies show that saffron can increase the capacity of antioxidant enzymes (GPX, SOD, GSH, and CAT) in animals. Other studies have also shown the effect of saffron on diabetes, which are listed in Table 1.

Table 1
Characteristics of studies that reported the potential roles of saffron on diabetes.

Type of study	Authors/date	Number and type of subjects	Dosage and type of administration/Model	Study duration	Main outcomes
Invitro	Mousavi, Tayarani [1]	PC12 cells	Saffron 5 and 25 μM/ml Crocin 10 and 50 μM	96 h	Significant decrease: ROS production Significant increase: GSH
	Li, Liu [2]	RAW264.7 cells	Crocin 0.1, 0.5 and 1 μM	24 h	Significant decrease: ROS production Significant increase: SOD
	Suh, Chon [3]	RAW264.7 cells	Crocin 5 and 20 μM	24 h	Significant decrease: Mitochondrial superoxide
	Yang, Huo [4]	BV-2 and N9 cells	Crocin 0.1 and 1 μM	24 h	Significant decrease: iNOS
Animal	Hemmati, Zohoori [5]	Type 2 diabetic rats (n = 10)	Saffron 25 and 100 mg kg orally	21 days	Significant increase: TAC Significant decrease: MDA
	Margaritis, Angelopoulou [6]	Type 2 diabetic rats (n = 12)	Crocin 25 and 50 mg kg orally	4 weeks	Significant increase: GSH, SOD, TAC Significant decrease: Protein carbonyls
	Delkhosh-Kasmaie, Farshid [7]	Type 2 diabetic rats (n = 18)	Safranal 0.025, 0.1 and 0.4 mg/kg i.p	37 days	Significant increase: SOD Significant decrease: MDA
	Kianbakht and MOZAFARI [8]	Type 2 diabetic rats (n = 90)	Saffron 25, 100 and 250 mg/kg orally Safranal 2.5, 5 and 10 ml/kg orally Crocin 2.5, 5 and 10 mg/kg orally	30 min before administration of indomethacin	Significant increase: GSH Significant decrease: MDA
	Hasanpour, Ashrafi	Type 2 diabetic rats (n = 10)	Saffron 200 mg kg I.P.	5 weeks	Significant increase: CAT and GPx Insignificant change: MDA
	Mohammad, Daryoush [10]	Type 2 diabetic rats (n = 10)	Saffron 40 mg/kg b.w./day, i.p.	8 weeks	Significant increase: GSH, SOD, CAT and GSH-Px Significant decrease: MDA
	Samaha, Said [11]	Type 1 diabetic rats (n = 6)	Crocin 10 mg/kg orally	8 weeks	Significant increase: GSH, SOD, CAT and TAC Significant decrease: MDA
	Kapucu [12]	Type 1 diabetic rats (n = 7)	Crocin 50 mg/kg i.p.	21 days	Significant increase: SOD, TOC and TAC Significant decrease: MDA
	Altinzo, Oner [13]	Type 2 diabetic rats (n = 10)	Crocin 20 mg/kg orally	21 days	Significant increase: GSH Significant decrease: MDA, XO
	Ahmadi, Rajaei [14]	Type 2 diabetic rats (n = 21)	Crocin 15, 30 and 60 mg/kg i.p	6 weeks	Significant decrease: MDA, TBARS
	Yaribeygi, Noroozadeh [15]	Type 2 diabetic rats (n = 6)	Crocin 40 mg/kg/i.p	8 weeks	Significant increase: SOD, CAT Significant decrease: MDA Insignificant changes: GLT
	Sefidgar, Ahmadi-Hamedani [16]	Type 2 diabetic rats (n = 12)	Crocin 40 and 60 mg/kg/day i.p	28 days	Significant increase: TAS Significant decrease:
	Bayatpoor, Mirzaee [17]	Type 2 diabetic rats (n = 18)	Crocin 20 mg/kg/day i.p	60 days	Significant increase: RAGE
	Tamaddonfard, Farshid [18]	Type 2 diabetic rats (n = 24)	Crocin 7.5, 15 and 30 mg/kg i.p	21 days	Significant increase: TAC Significant decrease: MDA
	Yaribeygi, Mohammadi [19]	Type 2 diabetic rats (n = 6)	Crocin 40 mg/kg/day i.p	8 weeks	Significant increase: SOD, CAT Significant decrease: MDA

Table 1 (*continued*)

Type of study	Authors/date	Number and type of subjects	Dosage and type of administration/Model	Study duration	Main outcomes
					Insignificant changes: GSH
	Abou-Hany, Atef [20]	type-1 diabetic rats (n = 10)	Crocin 20 mg/kg, orally	8 weeks	Significant increase: SOD, GSH Significant decrease: MDA
	Bahmani, Bathaie [21]	Type 2 diabetic rats (n = 10)	Crocin 100 mg/kg b.w orally	8 weeks	Significant increase: FRAP, SOD, GSH and CAT Significant decrease: MDA, NO
	Hazman and Ovalı	Type 2 diabetic rats fed a HFD (n = 8)	Safranal 0.2 ml/kg i.p	4 weeks	Significant decrease: TOS Significant increase TAS
	Motamedrad, Shokouhifar [23]	Type 2 diabetic rats/STZ (n = 14)	Saffron 25 and 100 mg/kg orally	21 days	Significant decrease: MDA Significant increase TAC
	Altinoz, Oner [24]	Type 2 diabetic rats/STZ (n = 10)	Saffron 20 mg/kg/day orally	21 days	Significant increase: GSH Significant decrease: MDA, XO
	Qiu, Jiang [25]	Type 2 diabetic mice/STZ (n = 12)	Crocin 50 mg/kg orally	8 weeks	Significant decrease: ROS, MDA Significant increase SOD, GSH and CAT Nrf2,HO-1 expression
	Samarghandian, Afshari [26]	Type 2 diabetic rats/STZ (n = 24)	Safranal 20,40 and 80 mg mg/kg/day i.p	4 weeks	Significant decrease: NO, MDA Significant increase SOD, GSH and CAT
	Altinoz, Oner [27]	Type 1 diabetic rats/STZ (n = 10)	Saffron 20 mg/kg/day i.p	21 days	Significant increase: SOD,CAT, GSH Significant decrease: MDA, XO
	Samarghandian, Azimi-Nezhad [28]	Type 2 diabetic rats/STZ (n = 27)	Saffron 10, 20 and 40 mg/kg i.p	4 weeks	Significant decrease: NO, MDA Significant increase SOD, GSH and CAT
	Rahbani, Mohajeri [29]	Type 2 diabetic rats/(n = 10)	Saffron 40 mg/kg i.p	8 Weeks	Significant decrease: MDA Significant increase: SOD, GPX, GSH, CAT

CAT; Catalase, GSH; Reduced Glutathione, GR; Glutathione reductase, iNOS; Inducible nitric oxide synthase, MAPK; p38 mitogen-activated protein kinase, MDA; Malondialdehyde, NF-κB: Nuclear factor-κB, JNK; Jun N-terminal kinase, NO; Nitric oxide, Nrf2; The nuclear factor erythroid 2–related factor 2, TBARS; Thiobarbituric acid reactive substances, advanced glycation end products, TAS; Total anti-oxidant capacity TOS; Total oxidative capacity ROS; Reactive oxygen species XO; xanthine oxidase.

4.5. Findings from the clinical trial studies

4.5.1. The effect of saffron on oxidative stress in diabetic patients

Two human studies had examined the effect of saffron on oxidative stress indices in patients with type 2 diabetes. Azimi, Ghiasvand et al. [70]demonstrated that saffron (1 g/day) significantly decreased F2-isoprostan in type 2 diabetic patients after eight weeks. Ebrahimi, Sahebkar et al. [20] in a randomized controlled trial, investigated the impact of saffron supplementation on oxidative stress in T2DM. In their study, 90 diabetic patients were enrolled; 45 subjects received a placebo and 45 patients received saffron at a dose of 100 mg/day (group 2), for 12 weeks. They reported that saffron significantly decreased MDA and also significantly increased TAC compared to the placebo group (Table 2).

5. Discussion

In this review, we evaluated 31 studies to investigate the role of saffron in the oxidative stress index in diabetes and hyperglycemia. The results of theses tudies showed that saffron can reduce oxidative stress in diabetes. Findings of in-vitro and animal studies showed that saffron supplementation has an effective role in reducing the levels of MDA, TBARS, and other indicators of lipid peroxidation. In addition, the results of clinical trials showed that saffron supplementation reduced products caused by oxidative stress and increased antioxidant enzymes. Oxidative stress and ROS have an important role in the development of complications of diabetes [71, 72]. In addition, increase in production of ROS and inflammation leads to insulin resistance and microvascular and macrovascular complications of diabetes [73, 74]. Therefore, by reducing oxidative stress and hyperglycemia, we can prevent the complications of diabetes [75]. Several mechanisms have been proposed for the possible role of saffron in reducing oxidative stress and improving antioxidant enzymes. Bahmani, Bathaie [56] showed that saffron significantly increased antioxidant enzymes in diabetic rats. In general, saffron reduces ROS production by interfering with ROS-related pathways, and ultimately reduces oxidative stress [50]. Saffron and its extracts contain many active ingredients such as beta-carotenes, picrocrocin, safranal, crocetin, and crocin, which can have therapeutic effects on a wide range of diseases such as metabolic syndrome and diabetes [76, 77]. Many studies show that saffron reduces lipid peroxidation factors such as MDA by increasing the antioxidant enzyme and reducing the production of

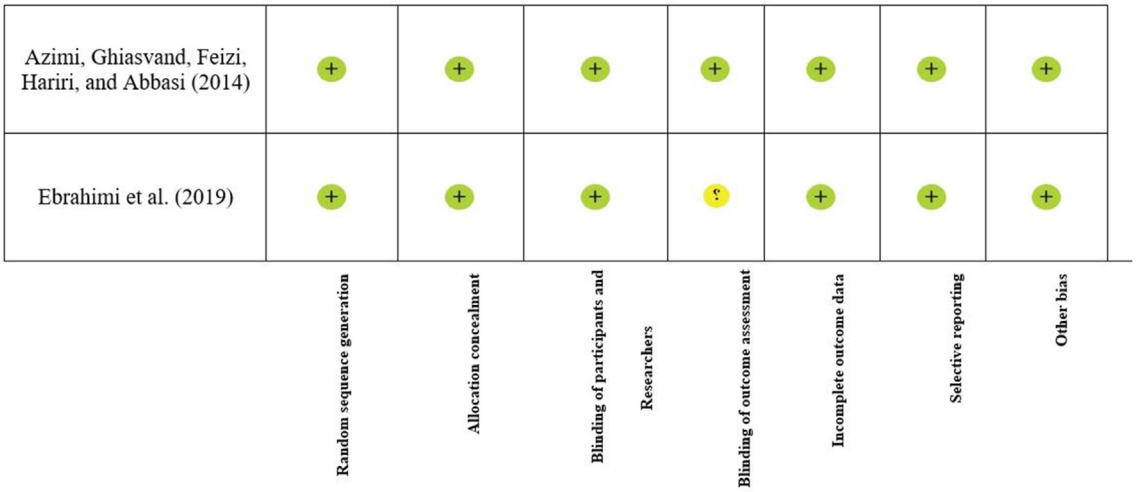

Fig. 2. Result of risk of bias assessment for human studies.

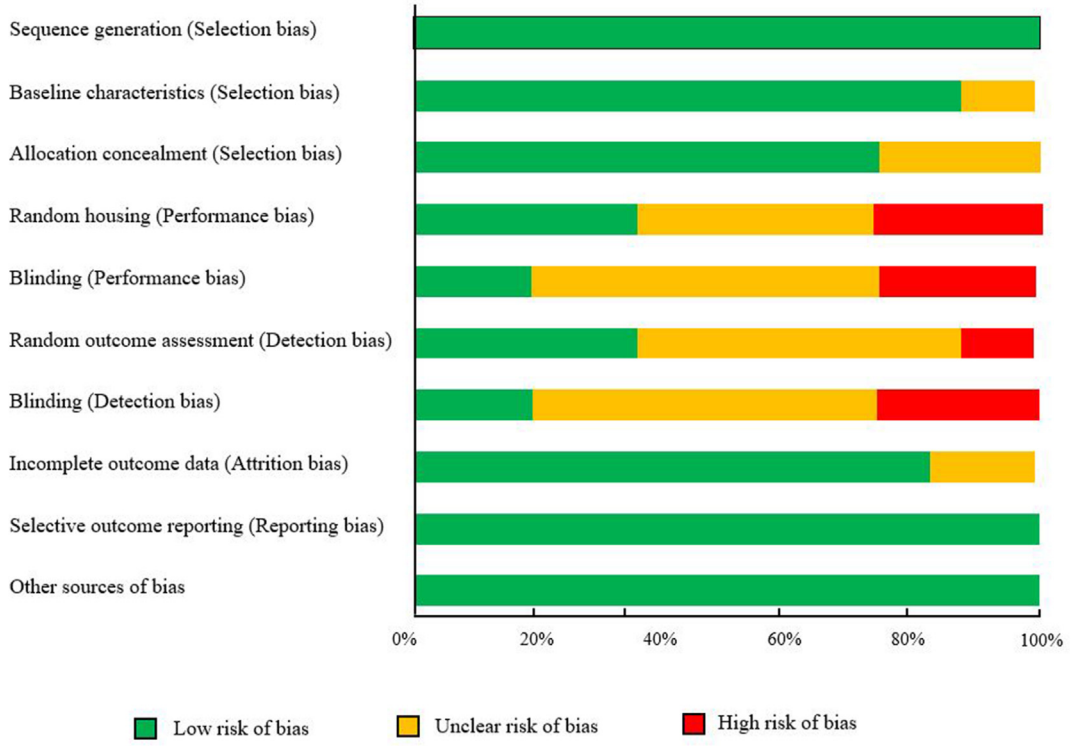

Fig. 3. SYRCLE's tool for assessing risk of bias in animal study.

ROS [27, 54]. Glutathione is present in two forms oxidized (GSSG) and, reduced (GSH) [78]. Increased GSSG to GSH ratio indicates cellular oxidative stress [79, 80]. GSH is a powerful antioxidant and protects important cellular components (such as beta cells) versus reacting with oxygenated functional groups such as peroxides and free radicals [80, 81]. Rahbani, Mohajeri [52] showed that saffron for eight weeks significantly increased GSH, and reduced MDA. Saffron increases NADPH by increasing the activity of glucose-6-phosphate dehydrogenase (G6PD). This increase in NADPH combined with glutathione reductase activity leads to the conversion of GSSG to GSH, thereby reducing oxidative stress [69, 82, 83].

Also, saffron increases Nrf-2 expression in response to ROS. Nrf-2 is a transcription factor expressed by the NFE2L2 gene [84, 85]. This molecule is a basic leucine-zipper protein that regulates the

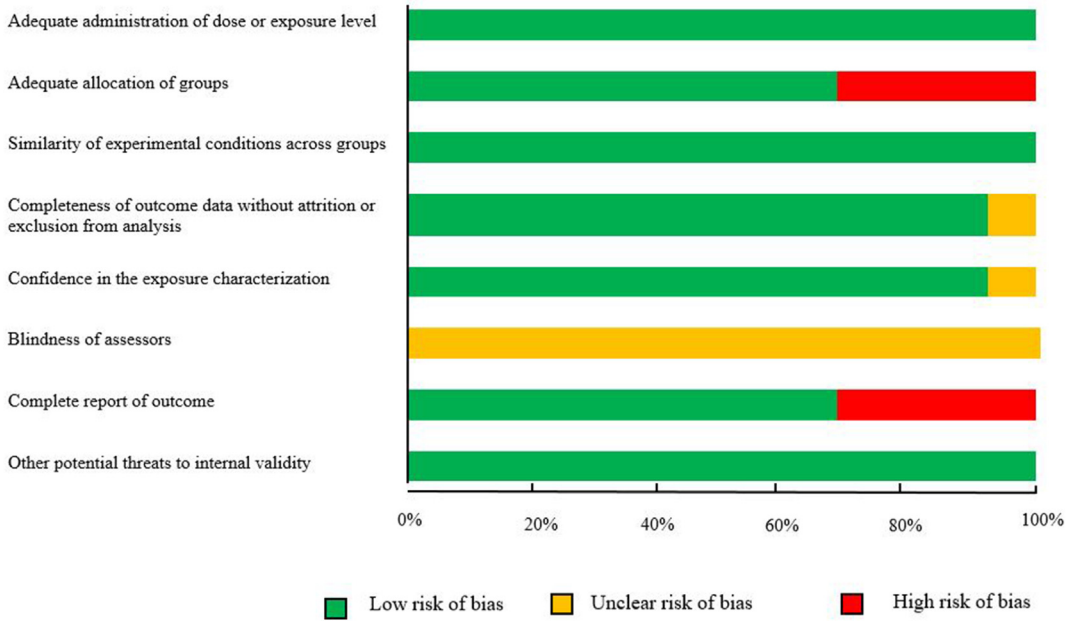

Fig. 4. Result of risk of bias assessment for *in vitro* studies included in the current systematic review.

Table 2
Summary of the human studies on the effect of saffron on oxidative indices in diabetes.

Authors, Date	Number and type of subjects	Sample Size	Age	Dosage and type of administration	sources	Study duration	Maine outcome
Azimi, Ghiasvand, Feizi, Hariri, and Abbasi (2014)	Human with type 2 diabetes (n = 42)	204	≥30	Saffron 1 g/day, orally/	Iran	8 weeks	Significant decrease: F2-isoprostan
Ebrahimi et al. (2019)	Human with type 2 diabetes (n = 40)	90	<56	Saffron 100 mg/day, orally	Iran	12 weeks	Significant decrease: MDA significant increase TAC

MDA; Malondialdehyde TAC; total antioxidant capacity.

expression of genes responsible for the phase 2 cell enzymes and the production of antioxidant enzymes through activation of the antioxidant response elements (ARE) [86, 87]. Saffron in conditions of oxidative stress by increasing the expression of Nrf-2, causes it to separate from the Kelch-like ECH-associated protein (Keap1) subunit to be transferred into the nucleus [27]. In the nucleus, Nrf-2 binds to the ARE subunit to increase the expression of antioxidant enzymes including, SOD, GPx, heme oxygenase-1 (HO-1), and NAD (P) H dehydrogenase quinone 1(NQO1) to eliminate reactive oxygen species [88]. On the other hand, saffron, by increasing the expression of the Nrf2 pathway, prevents phosphorylation of kappa light polypeptide gene enhancer in β-cells inhibitor, alpha (IκBα) by I kappa B kinase-a (IKK) and reduces the expression of NF-κB, as a result, reduces the damage caused by oxidative stress and the inflammatory response in diabetes mellitus [27, 88]. Also, increase in insulin sensitivity in different parts of the body such as skeletal muscle, can reduce oxidative stress caused by chronic hyperglycemia [70, 89]. Saffron reduces blood glucose by amplifying glucose uptake into cells, improving insulin signaling in insulin-sensitive tissues (adipose tissue and muscle) and increasing glucose transporter type 4 (GLUT-4) into cell membranes. Saffron increases the expression of 5′ AMP-activated protein kinase (AMPK) signaling pathway, leading to further transfer of glucose transporter type 4 (GLUT-4) to cell membranes [90]. AMPK has a significant effect on insulin sensitivity and glucose uptake in diabetes [91].Kang, Lee [91] have shown that saffron induced hypoglycemic effects by enhancing GLUT4 translocation into the plasma membrane via the AMPK/ACC pathway [91, 92]. AMPK can also reduce oxidative stress by increasing the expression of antioxidants in diabetes mellitus [70, 93].

6. Strength and limitations of the studies included

One of the strengths of this studies is the existence of animals and in-vitro studies. The advantage of these studies is that they are physiologically controllable. The existence of a control group in animal studies is another advantage of these studies that allows comparison between groups. The duration of interventions (3 to 12 weeks) was acceptable in the included studies. However, some of the limitations included the small number of clinical trials available in this analysis. Human studies provide the most accurate and conclusive data on the possibility and generalization of drug interactions in clinical treatments. The effects of drugs in humans are not exactly as the same as in animal or cell line models thorough differences in energy intake, intestinal morphology, and nutrient uptake. The human body's physiological and metabolic responses to drugs are different from those of other animals. Also doses and duration of interventions are different in the studies.

7. Conclusion

The findings of this systematic study show that saffron administration can be useful in reducing oxidative stress and increasing antioxidant enzymes. Also corcin, safranal, and crocetins main saffron compounds can decrease oxidative stress and increases antioxidant enzymes in diabetic conditions. However, for more

reliable conclusion about the antioxidant properties of saffron, more studies are needed, especially in the human field.

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Author contributions

The authors' responsibilities were as follows: AK, AM, and RND wrote the original paper; AK, AM, and RND contributed to data collection; AK provided advice and consultation; RND contributed to the final revision of the manuscript. All authors read and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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References

[1] Ceriello A, Prattichizzo F, Phillip M, Hirsch IB, Mathieu C, Battelino T. Glycaemic management in diabetes: old and new approaches. Lancet Diabetes Endocrinol 2022 Jan 1;10(1):75–84.
[2] Kooshki F, Reza Niazkar H, Shiraz S, Asghari Azar V, Moghimian M, Karimi A. Fumaria parviflora improves liver damage and lipid profile changes in STZ-induced diabetic rats. J Physiol Pharmacol 2020;24(3):221–9.
[3] Kooshki F, Tutunchi H, Vajdi M, Karimi A, Niazkar HR, Shoorei H, et al. A Comprehensive insight into the effect of chromium supplementation on oxidative stress indices in diabetes mellitus: a systematic review. Clin Exp Pharmacol Physiol 2021;48(3):291–309.
[4] Tinajero MG, Malik VS. An update on the epidemiology of type 2 diabetes: a global perspective. J Clin Endocrinol Metab 2021 Sep 1;50(3):337–55.
[5] Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. Diabetes Care 2011;34(6):1249–57.
[6] Qi L, Liang J. Interactions between genetic factors that predict diabetes and dietary factors that ultimately impact on risk of diabetes. Curr Opin Lipidol 2010;21(1):31.
[7] Blair M. Diabetes mellitus review. Urol Nurs 2016;36(1).
[8] Saracoğlu G, Baş H, Pandır D. Furan-induced cardiotoxicity in diabetic rats and protective role of lycopene. J Food Biochem 2019;43(3):e12738.
[9] Karimi A, Niazkar HR, Azar PS, Tutunchi H, Karimi M, Asghariazar V, et al. Protective effect of hydro-alcoholic extract of achillea millefolium on renal injury and biochemical factors in streptozotocin-induced diabetic rats. Nutr Food Sci 2021 May 18;51(7):1068–83. https://doi.org/10.1108/NFS-11-2020-0437.
[10] Folli F, Corradi D, Fanti P, Davalli A, Paez A, Giaccari A, et al. The role of oxidative stress in the pathogenesis of type 2 diabetes mellitus micro-and macrovascular complications: avenues for a mechanistic-based therapeutic approach. Curr Diabetes Rev 2011;7(5):313–24.
[11] Marcovecchio L. Complications of acute and chronic hyperglycemia. 2017.
[12] Keane KN, Fernandes Cruzat V, Carlessi R, Ivo Homem de Bittencour P, Newsholme P. Molecular events linking oxidative stress and inflammation to insulin resistance and β-cell dysfunction. Oxid Med Cell Longev 2015;2015.
[13] Fazelian S, Paknahad Z, Khajehali L, Kheiri S, Amani R. The effects of supplementation with vitamin D on inflammatory biomarkers, omentin, and vaspin in women with type 2 diabetes: a randomized double-blind placebo-controlled clinical trial. J Food Biochem 2018;42(6):e12631.
[14] Liu Z, Ren Z, Zhang J, Chuang CC, Kandaswamy E, Zhou T, et al. Role of ROS and nutritional antioxidants in human diseases. Front physiol 2018;9.
[15] Gerber PA, Rutter GA. The role of oxidative stress and hypoxia in pancreatic beta-cell dysfunction in diabetes mellitus. Antioxidants Redox Signal 2017;26(10):501–18.
[16] Cradock KA, ÓLaighin G, Finucane FM, Gainforth HL, Quinlan LR, Ginis KAM. Behaviour change techniques targeting both diet and physical activity in type 2 diabetes: a systematic review and meta-analysis. Int J Behav Nutr Phys Activ 2017;14(1):1–17.
[17] Gilis-Januszewska A, Lindström J, Tuomilehto J, Piwońska-Solska, B, Topór-Mądry R, Szybiński Z, et al. Sustained diabetes risk reduction after real life and primary health care setting implementation of the diabetes in Europe prevention using lifestyle, physical activity and nutritional intervention (DE-PLAN) project. BMC Publ Health 2017;17(1):198.
[18] Naceiri Mrabti H, Bouyahya A, Naceiri Mrabti N, Jaradat N, Doudach L, Faouzi ME. Ethnobotanical survey of medicinal plants used by traditional healers to treat diabetes in the taza region of Morocco. Evid Bas Comp Alternat Med 2021:2021.
[19] Meshesha SG, Yeshak MY, Gebremedhin GB, Tilahun Z, Fenta TG. Concomitant use of herbal and conventional medicines among patients with diabetes mellitus in public hospitals of Addis Ababa, Ethiopia: a cross-sectional study. Evid Bas Comp Alternat Med 2020;2020.
[20] Ebrahimi F, Sahebkar AH, Aryaeian N, Pahlavani N, Fallah S. Effects of saffron supplementation on inflammation and metabolic responses in type 2 diabetic patients: a randomized, double-blind, placebo-controlled trial. Diabetes, Metab Syndrome Obes Targets Ther 2019;12:2107.
[21] Tajaddini A, Roshanravan N, Mobasseri M, Aeinehchi A, Sefid-Mooye Azar P. Saffron improves life and sleep quality, glycaemic status, lipid profile and liver function in diabetic patients: a double-blind, placebo-controlled, randomised clinical trial. Int J Clin Pract 2021;75(8):e14334.
[23] Alavizadeh SH, Hosseinzadeh H. Bioactivity assessment and toxicity of crocin: a comprehensive review. Food Chem Toxicol 2014;64:65–80.
[24] Zhang A, Shen Y, Cen M, Hong X, Shao Q, Chen Y, et al. Polysaccharide and crocin contents, and antioxidant activity of saffron from different origins. Ind Crop Prod 2019;133:111–7.
[25] Hemmati M, Zohoori E, Mehrpour O, Karamian M, Asghari S, Zarban A, et al. Anti-atherogenic potential of jujube, saffron and barberry: anti-diabetic and antioxidant actions. EXCLI journal 2015;14:908.
[26] Samarghandian S, Azimi-Nezhad M, Farkhondeh T. Immunomodulatory and antioxidant effects of saffron aqueous extract (Crocus sativus L.) on streptozotocin-induced diabetes in rats. Indian Heart J 2017;69(2):151–9.
[27] Qiu Y, Jiang X, Liu D, Deng Z, Hu W, Li Z, et al. The hypoglycemic and renal protection properties of crocin via oxidative stress-regulated NF-κB signaling in db/db mice. Front Pharmacol 2020;11:541.
[28] Modaghegh M-H, Shahabiana M, Esmaeili HA, Rajbai O, Hosseinzadeh H. Safety evaluation of saffron (Crocus sativus) tablets in healthy volunteers. Phytomedicine 2008;15(12):1032–7.
[29] Caballero-Ortega H, Pereda-Miranda R, Abdullaev FI. HPLC quantification of major active components from 11 different saffron (Crocus sativus L.) sources. Food Chem 2007;100(3):1126–31.
[30] Wang C-Z, Calway T, Yuan C-S. Herbal medicines as adjuvants for cancer therapeutics. Am J Chin Med 2012;40(4):657–69.
[31] Shahi T, Assadpour E, Jafari SM. Main chemical compounds and pharmacological activities of stigmas and tepals of 'red gold'; saffron. Trends Food Sci Technol 2016;58:69–78.
[32] Hoshyar R, Mollaei H. A comprehensive review on anticancer mechanisms of the main carotenoid of saffron, crocin. J Pharm Pharmacol 2017;69(11):1419–27.
[33] Pandita D. Saffron (Crocus sativus L.): phytochemistry, therapeutic significance and omics-based biology. In: J. Medicinal aromat. Plants. Elsevier; 2021. p. 325–96.
[34] Konoshima T, Takasaki M, Tokuda H, Morimoto S, Tanaka E, Kawata E, et al. Crocin and crocetin derivatives inhibit skin tumour promotion in mice. Phytother Res: Int J Dev Pharmacolog Toxicolog Evaluat Nat Prod Deriv 1998;12(6):400–4.
[35] Gupta A, Pandey AK. Saffron and its active ingredients: a natural product with potent anticancer property. In: Drug development for cancer and diabetes. Apple Academic Press; 2020. p. 199–215.
[36] Moratalla N, José Bagur M, Lorenzo C, Martínez-Navarro, ME, Rosario Salinas M, Alonso GL. Bioactivity and bioavailability of the major metabolites of Crocus sativus L. Flower. MDPI; 2019.
[37] Samarghandian S, Borji A. Anticarcinogenic effect of saffron (Crocus sativus L.) and its ingredients. Pharmacogn Res 2014;6(2):99.
[38] Carmona M, Zalacain A, Salinas MR, Alonso GL. A new approach to saffron aroma. Crit Rev Food Sci Nutr 2007;47(2):145–59.
[39] Khilare V, Tiknaikb A, Prakash B, Ughadea B, Korhale G, Nalage D, et al. Multiple tests on saffron find new adulterant materials and reveal that Ist grade saffron is rare in the market. Food Chem 2019;272:635–42.
[40] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8(5):336–41.
[41] Higgins JP, Moher DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[42] Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol 2014;14(1):43.
[43] Rooney A. Extending a risk-of-bias approach to address in vitro studies. Washington, USA: National Toxicology Program Office of Health Assessment and Translation; 2015.
[44] Yang X, Liu B, Liu J, Chen T, Li J, Zhu Z, et al. Crocin inhibits oxidative stress and pro-inflammatory response of microglial cells associated with diabetic retinopathy through the activation of PI3K/Akt signaling pathway. J Mol Neurosci 2017;61(4):581–9.
[45] Suh KS, Chona S, Jung WW, Choi EM. Crocin attenuates methylglyoxal-induced osteoclast dysfunction by regulating glyoxalase, oxidative stress, and mitochondrial function. Food Chem Toxicol 2019;124:367–73.

[46] Mousavi SH, Tayarani N, Parsaee H. Protective effect of saffron extract and crocin on reactive oxygen species-mediated high glucose-induced toxicity in PC12 cells. Cell Mol Neurobiol 2010;30(2):185–91.
[47] Li S, Liu X, Lei J, Yang J, Tian P, Gao Y. Crocin protects podocytes against oxidative stress and inflammation induced by high glucose through inhibition of NF-κB. Cell Physiol Biochem 2017;42(4):1481–92.
[48] Altinoz E, Oner Z, Elbe H, Turkoz Y, Cigremis Y. Protective effect of saffron (its active constituent, crocin) on oxidative stress and hepatic injury in streptozotocin induced diabetic rats. Gene Ther Mol Biol 2014;16:160–71.
[49] Kapucu A. Crocin ameliorates oxidative stress and suppresses renal damage in streptozotocin induced diabetic male rats. Biotech Histochem 2020:1–8.
[50] Abou-Hany HO, Atef H, Said E, Elkashef HA, Salem HA. Crocin mediated amelioration of oxidative burden and inflammatory cascade suppresses diabetic nephropathy progression in diabetic rats. Chem Biol Interact 2018;284:90–100.
[51] Samaha MM, Said E, Salem HA. A comparative study of the role of crocin and sitagliptin in attenuation of STZ-induced diabetes mellitus and the associated inflammatory and apoptotic changes in pancreatic β-islets. Environ Toxicol Pharmacol 2019;72:103238.
[52] Rahbani M, Mohajeri D, Rezaie A, Nazeri M. Protective effect of ethanolic extract of saffron (dried stigmas of Crocus sativus L.) on hepatic tissue injury in streptozotocin-induced diabetic rats. J Anim Vet Adv 2012.
[53] Altinoz E, Oner Z, Elbe H, Cigremis Y, Turkoz Y. Protective effects of saffron (its active constituent, crocin) on nephropathy in streptozotocin-induced diabetic rats. Hum Exp Toxicol 2015;34(2):127–34.
[54] Motamedrad M, Shokouhifar A, Hemmati M, Moossavi M. The regulatory effect of saffron stigma on the gene expression of the glucose metabolism key enzymes and stress proteins in streptozotocin-induced diabetic rats. Res Pharm Sci 2019;14(3):255.
[55] Hazman Ö, Ovalı S. Investigation of the anti-inflammatory effects of safranal on high-fat diet and multiple low-dose streptozotocin induced type 2 diabetes rat model. Inflammation 2015;38(3):1012–9.
[56] Bahmani F, Bathaie SZ, Aldavood SJ, Ghahghaei A. Inhibitory effect of crocin (s) on Lens α-crystallin glycation and aggregation, results in the decrease of the risk of diabetic cataract. Molecules 2016;21(2):143.
[57] Yaribeygi H, Mohammadi MT, Sahebkar A. Crocin potentiates antioxidant defense system and improves oxidative damage in liver tissue in diabetic rats. Biomed Pharmacother 2018;98:333–7.
[58] Tamaddonfard E, Farshid AA, Asri-Rezaee S, Javadi SH, Khosravi V. Crocin improved learning and memory impairments in streptozotocin-induced diabetic rats. Iran J Basic Med Sci 2013;16(1):91.
[59] Bayatpoor ME, Bayatpoor ME, Mirzaee S, Karami Abd M, Mohammadi MT. Crocin treatment decreased pancreatic atrophy, LOX-1 and RAGE mRNA expression of pancreas tissue in cholesterol-fed and streptozotocin-induced diabetic rats. J Alternative Compl Med 2019;17(2).
[60] Sefidgar SM, Ahmadi-Hamedani M, Jebelli Javan A, Narenji R, Javaheri Vayghan A. Effect of crocin on biochemical parameters, oxidative/anti-oxidative profiles, sperm characteristics and testicular histopathology in streptozotocin-induced diabetic rats. Avicenna J Phytomed 2019;9(4):347.
[61] Yaribeygi H, Noroozadeh A, Mohammadi MT, Johnston TP, Sahebkar AH. Crocin improves oxidative stress by potentiating intrinsic anti-oxidant defense systems in pancreatic cells during uncontrolled hyperglycemia. J Pharmacopuncture 2019;22(2):83.
[62] Ahmadi M, Rajaei Z, Hadjzadeh MA, Nemati H, Hosseinia M. Crocin improves spatial learning and memory deficits in the Morris water maze via attenuating cortical oxidative damage in diabetic rats. Neurosci Lett 2017;642:1–6.
[63] Altinzo E, Oner Z, Elbe H, Vardi N. Neuro-protective effects of crocin on brain and cerebellum tissues in diabetic rats. Afr J Tradit, Complementary Altern Med 2014;11(6):33–9.
[64] Mohammad R, Daryoush M, Ali R, Yousef D, Mehrdad N. Attenuation of oxidative stress of hepatic tissue by ethanolic extract of saffron (dried stigmas of Crocus sativus L.) in streptozotocin (STZ)-induced diabetic rats. African J Pharm Pharmacol 2011;5(19):2166–73.
[65] Kianbakht S, Mozafari K. Effects of saffron and its active constituents, crocin and safranal, on prevention of indomethacin induced gastric ulcers in diabetic and nondiabetic rats. 2009.
[66] Delkhosh-Kasmaie F, Farshid AA, Tamaddonfar E, Imani M. The effects of safranal, a constitute of saffron, and metformin on spatial learning and memory impairments in type-1 diabetic rats: behavioral and hippocampal histopathological and biochemical evaluations. Biomed Pharmacother 2018;107:203–11.
[67] Margaritis I, Angelopoulou K, Lavrentiadou S, Mavrovouniotis LC, Tsantarliotou M, Taitzoglou L, et al. Effect of crocin on antioxidant gene expression, fibrinolytic parameters, redox status and blood biochemistry in nicotinamide-streptozotocin-induced diabetic rats. J Biolog Res-Thessaloniki 2020;27(1):1–15.
[68] Hasanpour M, Ashrafi M, Erjaee H, Nazifi S. The effect of saffron aqueous extract on oxidative stress parameters and important biochemical enzymes in the testis of streptozotocin-induced diabetic rats. J Physiol Pharmacol 2018;22(1):28–37.
[69] Samarghandian S, Afshari R, Sadati A. Evaluation of lung and bronchoalveolar lavage fluid oxidative stress indices for assessing the preventing effects of safranal on respiratory distress in diabetic rats. Sci World J 2014;2014.
[70] Azimi P, Ghiasvand R, Feizi A, Hariri M, Abbasi B. Effects of cinnamon, cardamom, saffron, and ginger consumption on markers of glycemic control, lipid profile, oxidative stress, and inflammation in type 2 diabetes patients. Rev Diabet Stud 2014;11(3):258.
[71] Zhang P, Li T, Wu X, Nice EC, Huang C. Oxidative stress and diabetes: antioxidative strategies. Front Med 2020:1–18.
[72] Ashish A, Shah A, Pandey S. Interaction between oxidative stress and diabetes: a mini-review. J Diabetes Metab Disord 2020;7:58–61.
[73] Aghadavod E, Soleimani A, Amirani E, Gholriz Khatami P, Akasheh N. Comparison between biomarkers of kidney injury, inflammation, and oxidative stress in patients with diabetic nephropathy and type 2 diabetes mellitus. Iran J Kidney Dis 2020;14(1).
[74] Mistry KN, Dabhi BK, Joshi BB. Evaluation of oxidative stress biomarkers and inflammation in pathogenesis of diabetes and diabetic nephropathy. Indian J Biochem Biophys 2020;57(1):45–50.
[75] Newsholme P, Fernandes Cruzat V, Noel Keane K, Carlessi R, Ivo Homem de Bittencourt P. Molecular mechanisms of ROS production and oxidative stress in diabetes. Biochem J 2016;473(24):4527–50.
[76] Yaribeygi H, Zare V, Butler AE, Barreto GE, Sahebkar AH. Antidiabetic potential of saffron and its active constituents. J Cell Physiol 2019;234(6):8610–7.
[77] Hosseini A, Razavi BM, Hosseinzadeh H. Pharmacokinetic properties of saffron and its active components. Eur J Drug Metab Pharmacokinet 2018;43(4):383–90.
[78] Bravo-Veyrat S, Hopfgartner G. High-throughput liquid chromatography differential mobility spectrometry mass spectrometry for bioanalysis: determination of reduced and oxidized form of glutathione in human blood. Anal Bioanal Chem 2018;410(27):7153–61.
[79] Couto N, Malys N, Gaskell SJ, Barber J. Partition and turnover of glutathione reductase from Saccharomyces cerevisiae: a proteomic approach. J Proteome Res 2013;12(6):2885–94.
[80] Lutchmansingh FK, Hsu JW, Bennett FI, Badaloo AV, McFarlane-Anderson N, Gordon-Strachan GM, et al. Glutathione metabolism in type 2 diabetes and its relationship with microvascular complications and glycemia. PLoS One 2018;13(6):e0198626.
[81] Ighodaro OM. Molecular pathways associated with oxidative stress in diabetes mellitus. Biomed Pharmacother 2018;108:656–62.
[82] Poma A, Gabriella F, Giuseppe C. Anti-inflammatory properties of drugs from saffron crocus. Anti-inflammatory & anti-allergy agents in medicinal chemistry (formerly current medicinal chemistry-anti-Inflammatory and Anti-Allergy Agents). ingentaconnect; 2012. p. 37–51. 11(1).
[83] El-Tahawy N, Said U. Effect of aqueous extract of saffron (crocus sativus L.) against gamma radiation-induced skeletal muscles damage in rats. EJRSA 2010;23(1):43–57.
[84] Kooshki F, Fardin F, Karimi A, Niazkar HR, Khoshbaten M, Maleki V, et al. Chromium picolinate balances the metabolic and clinical markers in nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled trial. Eur J Gastroenterol Hepatol 2020.
[85] Tsai CL, Tsai CW, Chang WS, Lin JC, Shih LC, He JL, et al. Protective effects of crocetin on arsenic trioxide-induced oxidative stress in human umbilical vein endothelial cells. In Vivo 2021 Nov 1;35(6):3157–63.
[86] David JA, Rifkin WJ, Rabbani PS, Ceradini DJ. The Nrf2/Keap1/ARE pathway and oxidative stress as a therapeutic target in type II diabetes mellitus. J Diabetes Res 2017;2017.
[87] Morvaridzadeh M, Agah S, Dulce Estevao M, Hosseini AS, Heydari H, Toupchian O, et al. Effect of saffron supplementation on oxidative stress parameters: a systematic review and meta-analysis of randomized placebo-controlled trials. Food Sci Nutr 2021 Oct;9(10):5809–19.
[88] Efentakis P, Rizakou A, Christodoulou E, Chatzianastasiou A, López MG, León R, et al. Saffron (Crocus sativus) intake provides nutritional preconditioning against myocardial ischemia–reperfusion injury in Wild Type and ApoE (−/−) mice: involvement of Nrf2 activation. Nutr Metabol Cardiovasc Dis 2017;27(10):919–29.
[89] Fabbrini E, Serafini M, Colic Baric I, Hazen SL, Klein S. Effect of plasma uric acid on antioxidant capacity, oxidative stress, and insulin sensitivity in obese subjects. Diabetes 2014;63(3):976–81.
[90] Dehghan F, Hajiaghaalipour F, Yusof A, Muniandy S, Hosseini SA, Heydari S, et al. Saffron with resistance exercise improves diabetic parameters through the GLUT4/AMPK pathway in-vitro and in-vivo. Sci Rep 2016;6:25139.
[91] Kang C, Lee H, Jung ES, Seyedian R, Jo M, Kim J, et al. Saffron (Crocus sativus L.) increases glucose uptake and insulin sensitivity in muscle cells via multipathway mechanisms. Food Chem 2012;135(4):2350–8.
[92] Farkhondeh T, Samarghandian S. The effect of saffron (Crocus sativus L.) and its ingredients on the management of diabetes mellitus and dislipidemia. African J Pharm Pharmacol 2014;8(20):541–9.
[93] Abedimanesh N, Motlagh B, Abedimanesh S, Bathaie SZ, Separham A, Ostadrahimi AR. Effects of crocin and saffron aqueous extract on gene expression of SIRT1, AMPK, LOX1, NF-κB, and MCP-1 in patients with coronary artery disease: a randomized placebo-controlled clinical trial. Phytother Res 2020;34(5):1114–22.