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REVIEW ARTICLE

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Antidiabetic potential of saffron and its active constituents

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Abstract

The prevalence of diabetes mellitus is growing rapidly worldwide. This metabolic disorder affects many physiological pathways and is a key underlying cause of a multitude of debilitating complications. There is, therefore, a critical need for effective diabetes management. Although many synthetic therapeutic glucose-lowering agents have been developed to control glucose homeostasis, they may have unfavorable side effects or limited efficacy. Herbal-based hypoglycemic agents present an adjunct treatment option to mitigate insulin resistance, improve glycemic control and reduce the required dose of standard antidiabetic medications. Saffron (*Crocus sativus* L.), whilst widely used as a food additive, is a natural product with insulin-sensitizing and hypoglycemic effects. Saffron contains several bioactive β carotenes, which exert their pharmacological effects in various tissues without any obvious side effects. In this study, we discuss how saffron and its major components exert their hypoglycemic effects by induction of insulin sensitivity, improving insulin signaling and preventing β-cell failure, all mechanisms combining to achieve better glycemic control.

KEYWORDS

crocin, *Crocus sativus*, diabetes mellitus, inflammation, insulin signal transduction, oxidative stress, saffron, safranal

1 | INTRODUCTION

The incidence of diabetes mellitus (DM) is growing worldwide (Mayer-Davis et al., 2017). Estimations suggest that the prevalence of DM will increase from 14% in 2010 to about 21% by 2050 in the US adult population (Boyle, Thompson, Gregg, Barker, & Williamson, 2010). However, it is possible that the overall prevalence of DM will increase to about 33% in 2050 if the current trajectory continues (Boyle et al., 2010). DM is the most prevalent metabolic disorder and the underlying cause of many complications related to morbidity and mortality (Boyle et al., 2010).

Uncontrolled diabetes can impair proper functioning of tissues and organs by activation of pathophysiological mechanisms such as oxidative stress, apoptosis, protein kinase c (PKC) isoforms, transcription factors, and inflammation (Domingueti et al., 2016; Yaribeygi, Atkin, & Sahebkar, 2018). These events can lead to debilitating complications such as diabetic nephropathy (DN), diabetic retinopathy, diabetic neuropathy, atherosclerosis, dementia, and cardiovascular

disorders (Gonzalez-Reyes, Aliev, Avila-Rodrigues, & Barreto, 2016; Maksimov et al., 2016; Putta, Peluso, et al., 2017; Yaribeygi, Atkin, et al., 2018). DN is the leading cause of hemodialysis, and diabetes-induced cardiovascular problems are a major cause of death among diabetic patients (Yaribeygi, Butler, Barreto, & Sahebkar, 2018; Yaribeygi, Taghipour, & Taghipour, 2014). Similarly, diabetes-induced retinopathy is major cause of blindness (Nentwich & Ulbig, 2015). There is, therefore, an ever increasing need to optimize the management of diabetes (Schaper et al., 2016).

Several classes of synthetic antidiabetic agents such as insulin, sulfonylureas, dipeptidyl peptidase 4 inhibitors, thiazolidinediones, biguanides, sodium-glucose cotransporter type 2 inhibitors, glucagon-like peptide-1 receptor agonists and α-glucosidase inhibitors are currently available (Yaribeygi, Butler, et al., 2018). These drugs are highly effective as hypoglycemic agents, but may have unfavorable side effects (Chaudhury et al., 2017). Thus, the use of herbal-based antidiabetic agents as well as "nutraceuticals" is an attractive option, as they generally are lower in cost, easily available, and often have a better safety profile (Eddouks, Bidi, El Bouhali, Hajji, & Zeggwagh, 2014; Garg, 2016).

The use of nutraceuticals, defined as nutrient agents which show beneficial properties on human health and are composed of different plant-derived nutrients as well as some vitamins and biochemical compounds, is growing (Riya et al., 2014). The evidence suggests that some nutraceuticals have potent hypoglycemic effects, lowering blood glucose by activating molecular mechanisms (Garg, 2016; Putta, Yarla, et al., 2017; Riya et al., 2014; Saleem, Sarkar, Ankolekar, & Shetty, 2017). One such nutraceutical is saffron (*L-Crocus sativus*) which not only exerts a hypoglycemic effect but also shows antioxidant and anti-inflammatory properties (Sarfarazi, Jafari, & Rajabzadeh, 2015). Saffron exerts its hypoglycemic effects through several molecular mechanisms (Sarfarazi et al., 2015). Here, we review the literature regarding the hypoglycemic actions of the nutraceutical saffron and its constituents.

2 | GLUCOSE TRANSPORT ACROSS THE CELL MEMBRANE AT A GLANCE

Glucose is a hydrophilic molecule with a high molecular weight of 180, and requires carriers to pass through cell membranes (Hall, 2015). Glucose has two primary ways to enter cells: (a) active cotransport by a sodium dependent mechanism and (b) passive-facilitation via carriers (independent of sodium; Hall, 2015). Glucose transporters (GLUTs) are a class of proteins which provide bidirectional facilitated glucose transport across mammalian plasma membranes based upon the glucose concentration gradient and this is not therefore an energy consuming process (Chen & Lippincott-Schwartz, 2015; Hall, 2015). At least 14 members of the GLUT family have been identified in humans, labeled as GLUT-1 to GLUT-14; GLUT-1, GLUT-2, GLUT-3 and GLUT-4 are the most important in glucose homeostasis (Hall, 2015; Huang & Czech, 2007). GLUT-4 is an insulin-dependent isoform of the glucose carriers which, unlike the other isoforms, is entirely dependent upon insulin (Hall, 2015; Moraes-Vieira, Saghatelian, & Kahn, 2016). GLUT-4 has a molecular weight of 54800 D and is mainly expressed in adipocytes, cardiomyocytes, and skeletal muscle cells (Hall, 2015). GLUT-4 resides in cytoplasmic vesicles but, in response to insulin, translocates to the cell membrane and facilitates glucose entry into cells (Hall, 2015; Huang & Czech, 2007). Since skeletal muscle cells act as the main store for glucose (as glycogen), GLUT-4 plays a key role in whole body glucose homeostasis, especially in the postprandial state (Huang & Czech, 2007).

3 | INSULIN SIGNALING PATHWAYS

Insulin signal transduction (IST) is initiated by the binding of insulin to the insulin receptor (IR) which is composed of two chains, α and β (Færch et al., 2016). Ligand binding to the α chain of IR induces structural changes in the β chain by prompting auto-phosphorylation in tyrosine residues followed by downstream events such as recruitment of different adaptor proteins (Hall, 2015; Kiselyov, Versteyhe, Gauguin, & De Meyts, 2009). These events create a proper binding site for IR substrate type 1 (IRS-1; Kiselyov et al., 2009). Various insulin-dependent kinases, such as extracellular signal-regulated kinase 1/2 (ERK1/2), atypical PKC, S6K1, serine/threonine-protein kinase 2 (SIK2), AKT, mTOR, and ROCK1 can activate these binding sites by phosphorylating them (Copps & White, 2012; Kiselyov et al., 2009). Some kinases, AMP-activated protein kinase (AMPK) and glycogen synthase kinase 3, for example, phosphorylate IRSs and trigger downstream signal transduction independent of insulin (Copps & White, 2012). In the subsequent step, activated IRS-1 links to phosphoinositide 3-kinase and activates it which, in turn, catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate (PIP_2) to phosphatidylinositol 3,4,5-trisphosphate (PIP_3; Ho, Sriram, & Dipple, 2016). PIP_3 is itself a potent activator for PKB (protein kinase B, also known as Akt) which facilitates glucose entering into the cells by translocation of GLUT-4, and inhibits glycogen synthase kinase leading to more glycogen synthesis (Ho et al., 2016; Koeppen & Stanton, 2017).

4 | SAFFRON (*CROCUS SATIVUS* L.)

Saffron is a plant of the Iridaceae family, which is traditionally used as a food additive or spice (Yaribeygi, Sahraei, Mohammadi, & Meftahi, 2014). In addition to being a food coloring and aromatic spice, saffron has historically been used as a therapeutic agent; even in ancient documents, scientists such as Avicenna emphasized its potent therapeutic properties (Hosseinzadeh & Nassiri-Asl, 2013; Javadi, Sahebkar, & Emami, 2013). Saffron extracts contain several potent β carotenes, such as crocin, crocetin, picrocrocin, and safranal, and thus can exert pharmacological effects in a wide variety of tissues (Rahmani, Khan, & Aldebasi, 2017; Rameshrad, Razavi, & Hosseinzadeh, 2018). Crocin, picrocrocin, and safranal are the major active ingredients in

saffron, and account for the color, taste and odor, respectively, of this spice (Rahmani et al., 2017). The saffron plant is now cultivated worldwide, though 90% of world production is based in Iran (Ghorbani, 2008).

4.1 | Pharmacological effects of saffron

The active ingredients of saffron are able to exert antioxidant (Nikbakht-Jam et al., 2015; Rahiman, Akaberi, Sahebkar, Emami, & Tayarani-Najaran, 2018; Yaribeygi, Mohammadi, Rezaee, & Sahebkar, 2018), anti-inflammatory (Yaribeygi, Mohammadi, Rezaee, et al., 2018), memory enhancer (Abe & Saito, 2000; Ghadrdoost et al., 2011), antitumor (Hoshyar & Mollaei, 2017; Moradzadeh, Sadeghnia, Tabarraei, & Sahebkar, 2018), antidepressant (Jam et al., 2017; Lopresti & Drummond, 2014; Shafiee, Arekhi, Omranzadeh, & Sahebkar, 2017), antiasthma (Javadi, Sahebkar, & Emami, 2017), cough suppressant (El-Alfy, 2017), cardiovascular protection (Hatziagapiou & Lambrou, 2018; Sobhani, Nami, Emami, Sahebkar, & Javadi, 2017), neuroprotection (Wang et al., 2015), visual function improvement (Liou et al., 2018; Riazi et al., 2017) and sexual behavior potentiation effects (Malviya, Malviya, Jain, & Vyas, 2016; Sadoughi, 2017; Table 1). This evidence implies that the active compounds of saffron can alter molecular mechanisms by affecting transcription factors, growth factors and diverse intracellular signaling pathways (Samarghandian, Azimi-Nezhad, & Farkhondeh, 2016; Yang et al., 2017; Yaribeygi, Mohammadi, Rezaee, et al., 2018). Moreover, studies indicate the potent hypoglycemic effects of saffron and its bioactive ingredients/β carotenes (Shirali, Zahra Bathaie, & Nakhjavani, 2013). Improvement of the glycemic profile by saffron components can prevent diabetic complications by inhibition of hyperglycemia-induced pathophysiologic molecular pathways (Yaribeygi, Mohammadi, Rezaee, et al., 2018; Yaribeygi, Mohammadi, & Sahebkar, 2018). Saffron significantly lowers plasma glucose and insulin levels and effected improvement in the serum glycemic profile (Arasteh et al., 2010; Shirali et al., 2013).

4.1.1 | Hypoglycemic potential of saffron and its active ingredients

Saffron extracts have potent hypoglycemic effects, making them a primary nutraceutical for the treatment of both type 1 (insulin dependent) and type 2 (non-insulin dependent) diabetes (Milajerdi et al., 2018; Shirali et al., 2013). Saffron β carotenes can induce hypoglycemic effects via several pathways (Table 2).

Induction of insulin sensitivity and improvement of insulin signaling

Reduction of insulin sensitivity and an increase in insulin resistance in peripheral tissues is a central feature of diabetes (Yaribeygi, Katsiki, Behnam, Iranpanah, & Sahebkar, 2018). The peripheral insulin-dependent cells (adipocytes, muscular tissues, and cardiomyocytes) are therefore unable to take up circulating glucose and so insulin resistance develops (Yaribeygi, Katsiki, et al., 2018). Crocin, safranal and crocetin exert their hypoglycemic effects via induction of insulin sensitivity in insulin-dependent tissues (Kang et al., 2012). Kang et al. (2012) demonstrated that saffron markedly increased peripheral insulin sensitivity by phosphorylation of acetyl-CoA carboxylase (AMPK/ACC) and mitogen-activated protein kinases, but not PI3-kinase/Akt. Xi, Qian, Xu, Zheng, et al. (2007) demonstrated that

TABLE 1 Beneficial effects of saffron nutraceuticals

Classes of effects	Details of effects	References
Saffron ingredient effects		
Antioxidant	Prevention of oxidative stress by potentiation of antioxidative defenses, free radical scavenging	Yaribeygi, Mohammadi, and Sahebkar (2018)
Antidiabetes	Hypoglycemic effects by increasing insulin sensitivity, β-cell function and improvement in insulin signal transduction	Shirali et al. (2013) and Xi, Qian, Xu, Zho, et al. (2007)
Memory enhancer	Improvement in learning behavior, long-term potentiation and spatial memory	Abe and Saito (2000) and Ghadrdoost et al. (2011)
Gene protection	Protection against mutations and damage to DNA	Ashrafi et al. (2015)
Sexual-behavior potentiation	Improvement in sexual behavior and enhanced gonadal function	Malviya et al. (2016) and Sadoughi (2017)
Neuroprotection	Protection against neuronal damages in CNS and peripheral nerves by inhibition of injurious pathways	Wang et al. (2015)
Cough suppressant	Suppression of cough by centric pathways	El-Alfy (2017)
Antidepressant	Protection against depression and improvement in mood state by dopamine and serotonin release	Lopresti and Drummond (2014)
Anti-inflammation	Prevention of inflammatory mediator expression and inhibition of inflammatory responses	Yaribeygi, Mohammadi, and Sahebkar (2018)
Cardiovascular protection	Protection of the cardiovascular system from atherosclerosis and improvement of endothelial function	Hatziagapiou and Lambrou (2018)
Antitumor	Suppression of malignant cells by induction of apoptosis	Hoshyar and Mollaei (2017)

TABLE 2 Hypoglycemic effects of saffron ingredients

Hypoglycemic effects of saffron ingredients	Details	References
Improvement in insulin signaling/insulin sensitivity	Induces insulin sensitivity by improvement of insulin signaling via phosphorylation of AMPK/ACC; induction of the GLUT4/AMPK molecular pathway, downregulation of adiponectin and TNF-α, lowering of free fatty acids and triglycerides and improvement in the plasma lipid profile, prevention of oxidative stress, inhibition of PTP1B	Dehghan et al. (2016), Hazman et al. (2016), Kang et al. (2012), Xi et al. (2005), Xi, Qian, Xu, Zheng, et al. (2007), Xi, Qian, Xu, Zho, et al. (2007), and Yaribeygi, Katsiki, et al. (2018)
Improvement in β-cell function	Prevention of β-cell damage by inhibition of injurious pathways such as oxidative stress and inflammation, suppression of caspase-dependent β-cell damage, downregulation of p53 that is involved in β-cell apoptosis	Brownlee (2003), Elgazar et al. (2013), Elsherbiny et al. (2016), Ghorbanzadeh et al. (2017), Keane et al. (2015), Liadis et al. (2005), Lv et al. (2016), and Zhang et al. (2015)
Induction of GLUT4 expression/localization	Induction of GLUT4 translocation into the plasma membrane by AMPK/ACC and Akt kinase pathways as well as by insulin secretion	Du et al. (2018), Hazman et al. (2016), Maeda et al. (2014), Shirali et al. (2013), and Yaribeygi, Katsiki, et al. (2018)
Prevention of oxidative stress	Protection against oxidative stress-induced diabetes by potentiation of antioxidant elements and free radical scavenging	Hatziagapiou and Lambrou (2018), Hu et al. (2018), Kianbakht and Hajiaghaee (2011), Maritim et al. (2003), Yang et al. (2017), Yaribeygi, Faghihi, et al. (2018), Yaribeygi, Mohammadi, and Sahebkar (2018)
Suppression of inflammatory responses	Prevention of inflammatory mediator expression that is involved in insulin resistance	Black (2003), Navarro-González et al. (2011), Rajaei et al. (2013), and Wellen and Hotamisligil (2005)

Note. ACC: acetyl-CoA carboxylase; Akt: a form of protein kinase; AMPK: AMP-activated protein kinase; GLUT4: glucose transporter; PTP1B: protein tyrosine phosphatase 1B; TNF-α: tumor necrosis factor-α.

crocetin therapy in diabetic rats improved insulin sensitivity by downregulation of adiponectin, tumor necrosis factor-α (TNF-α) and leptin expression in white adipocytes at both the protein and messenger RNA (mRNA) level. They also reported that crocetin prevented dexamethasone-induced insulin resistance by lowering free fatty acids and triglycerides in plasma and by downregulation of TNF-α (Xi, Qian, Shen, Wen, & Zhang, 2005). Crocetin may also suppress adiponectin expression leading to increased insulin sensitivity (Xi, Qian, Xu, Zhou, & Sun, 2007).

Shirali et al. (2013) evaluated insulin sensitivity in diabetic animals by HOMA-IR (homeostatic model assessment for insulin resistance), finding that crocin significantly reduced glycosylated hemoglobin (HbA1C) and improved insulin sensitivity, probably by prevention of oxidative stress and improvement of the plasma lipid profile. Hazman, Aksoy, and Büyükben (2016) observed that crocin suppressed TNF-α and interleukin-1β (IL-1β) levels in plasma and the TNF-α and interferon-γ (IFN-γ) levels in pancreatic tissues and thereby improved insulin sensitivity. Dehghan et al. (2016) found that saffron improved the plasma glycemic profile by upregulation of the GLUT4/AMPK molecular pathway. Maeda, Kai, Ishii, Ishii, and Akagawa (2014) suggested that safranal acts as a potent inducer of IST by inhibition of protein tyrosine phosphatase 1B (PTP1B), which is a negative modulator of IST via tyrosine dephosphorylation of IRs. The active ingredients of saffron therefore exert their hypoglycemic effects via improving IST and inducing insulin sensitivity in peripheral tissues.

Improvement of β-cell function

β-Cell dysfunction is a central feature of diabetes (Fernández-Millán et al., 2015). Located in the islets of the pancreas, β cells are unique as they are able to secrete insulin in response to the increases in plasma glucose (Fernández-Millán et al., 2015). Many pathological mechanisms can impair the proper functioning of β cells, leading to an insufficient insulin secretory response, the underlying cause of DM (Keane, Cruzat, Carlessi, de Bittencourt, & Newsholme, 2015).

The evidence suggests that saffron extracts may improve β-cell function directly or indirectly via inhibition of pathophysiologic molecular mechanisms responsible for the destruction of β cells (Xi et al., 2005). Since hyperglycemia has a direct toxic effect on β cells, it may also be that saffron extract prevents β-cell toxicity/destruction by induction of insulin sensitivity and lowering of blood glucose (Brownlee, 2003). Xi et al. (2005) demonstrated that crocetin improved β-cell function and prevented dexamethasone-dependent insulin resistance and hyperglycemia. Elgazar, Rezq, and Bukhari (2013) reported that saffron extract prevented deterioration in β-cell function and induced islet regeneration, probably via its antioxidant effect, in alloxan-induced diabetic animals. Ghorbanzadeh, Mohammadi, Mohaddes, Dariushnejad, and Chodari (2017) found that crocin prevented diabetes-induced apoptosis in pancreatic β cells via downregulation of the p53 protein. Moreover, saffron nutraceuticals can prevent the impairment of β cells by inhibition of detrimental molecular mechanisms. Finally, the evidence links caspases with β-cell destruction and islet failure (Liadis et al., 2005). Caspases are a family of proteins involved in various forms of cellular death, such as

apoptosis, necrosis and pyroptosis (Zhang et al., 2015). Saffron extract can ameliorate caspase activity and prevent its injurious effects (Elsherbiny, Salama, Said, El-Sherbiny, & Al-Gayyar, 2016; Lv et al., 2016). Some mediators that are involved in necrotic pathways, such as TNF-α, may be suppressed by saffron nutraceuticals (Du et al., 2018).

Induction of GLUT-4 expression/localization

Saffron nutraceutical extract may improve glycemic control via an effect on GLUT-4 (Kang et al., 2012). Kang et al. (2012) demonstrated that saffron extract induced hypoglycemic effects via an increase of GLUT4 translocation into the plasma membrane via the AMPK/ACC pathway. Saffron extracts induced AMPK signaling pathways, leading to more GLUT-4 translocation into the cell membrane (Dehghan et al., 2016). Crocin and saffron extracts can also activate Akt kinase, which may result in GLUT-4 translocation from an intracellular pool to the plasma membrane of insulin-dependent tissues through IRs and PI3-kinase pathways (Hu et al., 2018). Saffron extracts may induce GLUT-4 translocation into cell membranes by improving β-cell function and stimulating insulin secretion, a potent inducer of GLUT-4 localization to the cell membrane (Shirali et al., 2013).

4.1.2 | Prevention of oxidative stress

Oxidative stress is a consequence of an imbalance between free radical species and the antioxidant defense system in favor of free radicals (Alexiou et al., 2018; Cabezas, El-Bachá, González & Barreto, 2012; Leszek et al., 2016; Sutachan et al., 2012; Yaribeygi, Faghihi, Mohammadi, & Sahebkar, 2018). Oxidative stress plays a key role in DM and its complications (Yaribeygi, Faghihi, et al., 2018). Free radical overload can disrupt normal glucose homeostasis and cause development of DM, as well as insulin resistance in peripheral tissues (Maritim, Sanders, & Watkins, 2003). Improvement of the redox state is therefore a major therapeutic goal (Yaribeygi, Faghihi, et al., 2018). Saffron nutraceuticals are potent antioxidant agents that can prevent oxidative damage in various tissues by scavenging free radicals or by potentiation of the antioxidant defense elements (Yang et al., 2017; Yaribeygi, Mohammadi, Rezaee, et al., 2018). Saffron extracts are able to ameliorate oxidative damage leading to β-cell dysfunction and insulin resistance and so improve glycemic control (Kianbakht & Hajiaghaee, 2011; Rajaei et al., 2013).

4.1.3 | Suppression of inflammatory responses

Inflammatory responses play a pivotal role in many diseases, including DM (Wellen & Hotamisligil, 2005). Inflammation is clearly linked to β-cell dysfunction and islet failure, insulin resistance and DM development (Black, 2003; Wellen & Hotamisligil, 2005). The pathophysiology of DM is characterized by activation of inflammatory pathways and upregulation of inflammatory mediators such as TNF-α and interleukin-6 (IL-6; Navarro-González, Mora-Fernández, De Fuentes, & García-Pérez, 2011). Saffron extracts have potent anti-inflammatory potential and can inhibit procytokines and inflammatory mediator expression at the mRNA and protein levels and prevent inflammatory responses in various tissues (Nam et al., 2010; Poma, Fontecchio, Carlucci, & Chichiriccò, 2012). Saffron prevents inflammation-induced insulin resistance by downregulation of the inflammatory mediators involved in insulin resistance and DM development (Samarghandian et al., 2016; Yaribeygi, Mohammadi, Rezaee, et al., 2018). Therefore, the active ingredients in saffron can improve glycemic control by inhibition of inflammation-induced insulin resistance in peripheral tissues and also by prevention of inflammation dependent β-cell damage (Samarghandian et al., 2016).

Clinical trial on the hypoglycemic effects of saffron

In addition to experimental studies, there is recent evidence regarding the hypoglycemic potential of saffron and its active ingredients in humans (Kermani et al., 2017; Milajerdi et al., 2018; Sepahi et al., 2018). Milajerdi et al. (2018) performed a randomized triple blind study in 54 type 2 diabetic patients and found that eight weeks of daily saffron consumption markedly reduced fasting blood glucose in these subjects. Sepahi et al. (2018) designed a placebo-controlled randomized clinical trial and found that daily administration of 15 mg of oral crocin markedly reduced HbA1C in diabetic patients compared to control placebo groups. Moreover, Milajerdi et al. (2016), in a triple-blind clinical trial study demonstrated that 15 mg of saffron for 8 weeks markedly reduced fasting and 2 hr postprandial blood glucose in type 2 diabetic patients. These studies provide clear experimental data supporting the hypoglycemic effects of saffron and its extracts. However, more clinical trials are still required. In all these trials, saffron or crocin were safe and well tolerated, with no serious adverse effects reported.

5 | CONCLUSION

Saffron has potent hypoglycemic effects. This nutraceutical can aid maintenance of glycemic control by improving IST, thus promoting insulin sensitivity. Saffron ingredients can improve β-cell function by inhibition of damaging pathways involved in β-cell failure that lead to insufficient insulin release. Saffron can also induce GLUT-4 translocation into the plasma membrane from the intracellular pool and so increase glucose uptake by insulin-dependent tissues. Saffron increases GLUT-4 localization in the plasma membrane via several pathways such as AMPK/ACC and Akt kinase activation, as well as by induction of insulin secretion. Moreover, saffron extracts improve glycemic control by suppression of the pathophysiologic pathways involved in insulin resistance, such as oxidative stress and inflammation. Extant evidence suggests that saffron is a safe and efficacious natural product that might serve as an adjunct to routine antidiabetic medications, and also as a dietary supplement to mitigate insulin resistance in prediabetic individuals.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest.

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