Saffron against Components of Metabolic Syndrome: Current Status and Prospective

Mojtaba Shafiei, Nazanin Sadat Aghili Moghaddam, Mohammad Nosrati, Mahsa Tousi, Mikhail Ryzhikov, Mohammad Reza Parizadeh, Hamid Fiuji, Majid Rajabian, Amirhossein Bahreyni, Majid Khazaei, and Seyed Mahdi Hassanian

ABSTRACT: Saffron, the dried stigmas of Crocus sativus L., is mainly used as a food coloring and flavoring agent. This agricultural product is used in traditional medicine for the treatment of several diseases including asthma, liver disease, menstruation disorders, and, of special interest in this review, metabolic syndrome. Saffron and its active components including crocin, crocetin, and safranal are potential therapeutic candidates for attenuating MetS complications including hypertension, hyperglycemia, obesity, and dyslipidemia. This review summarizes the protective role of saffron and its constituents in the pathogenesis of MetS for a better understanding and hence a better management of this disease.

KEYWORDS: saffron, natural food coloring, phytomedicine, metabolic syndrome

INTRODUCTION: Saffron, the world’s most expensive spice, belongs to the large family of Iridaceae and to the genus Crocus, which are primarily distributed in southwestern Asia and the Mediterranean. Iran is the major supplier of this spice, producing more than 90% of the world’s total annual saffron, followed by India (5%) and countries of the Mediterranean basin (Spain, Morroco, Greece, Italy, and Turkey). The optimal climatic conditions for better growth and development of this spice are rainy autumns, mild winters, and warm summers. A short flowering duration, the intensive labor hand for flavor picking and stigma separation, the increasing labor costs, and the high number of flowers (i.e., 150,000 to 200,000) required to produce 1 kg of pure dried saffron, all have made saffron production unprofitable.

Saffron has been used from ancient times as a spice in food and as a dye in perfumes and cosmetics preparation, due to the coloring, bitterness, and aromatic power of its dried stigmas. It has also been used in traditional medicine for a wide range of ailments including cramps, asthma, depression, liver disease, menstruation disorders, pain, and tumors. Saffron is comprised mainly of carbohydrates (63%) followed by protein (12%), moisture (10%), fat (5%), crude fiber (5%), minerals (5%), and vitamins (% w/w). Moreover, a variety of biologically active ingredients has been isolated from saffron. It is now well-known that crocin (monoglycosyl or diglycosyl esters of crocetin), crocetin (a natural carotenoid dicarboxylic acid precursor of crocin), picrocroc (monoterpene glycoside precursor of safranal), and safranal (the major organoleptic principle of the stigmas) comprise the four major bioactive compounds of saffron and are responsible not only for its sensory profile but also for its health-promoting properties. The structure of these active constituents is presented in Figure 1.

The therapeutic potency of saffron (Crocus sativus L.) has been extensively investigated for the treatment of several diseases including metabolic syndrome (MetS) (see Table 1). MetS is a common pathophysiologic condition characterized by a cluster of metabolic and cardiovascular disorders such as hyperglycemia, hypertension, dyslipidemia, and obesity. According to the International Diabetes Federation (IDF), around 20–25% of the world’s adult
<table>
<thead>
<tr>
<th>Authors</th>
<th>MetS component</th>
<th>Impairment cause</th>
<th>Agent</th>
<th>Dose (mg/kg)</th>
<th>Route</th>
<th>Species</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samarghandian et al.21</td>
<td>Insulin resistance, dyslipidemia</td>
<td>STZ</td>
<td>Saffron extract</td>
<td>40−80</td>
<td>IP</td>
<td>Rat</td>
<td>Saffron extract reduced hyperglycemia and hyperlipidemia risk and also reduced the oxidative stress in diabetic encephalopathy rats.</td>
</tr>
<tr>
<td>Rajaei et al.22</td>
<td>Insulin resistance</td>
<td>STZ</td>
<td>Crocin</td>
<td>15, 30, and 60</td>
<td>IP</td>
<td>Rat</td>
<td>Crocin at a dose of 60 mg/kg significantly reduced the blood glucose level in diabetic animals.</td>
</tr>
<tr>
<td>Mohjери et al.23</td>
<td>Insulin resistance</td>
<td>Alloxan</td>
<td>Saffron ethanolic extract</td>
<td>20, 40, and 80</td>
<td>Oral, IP</td>
<td>Rat</td>
<td>Saffron ethanolic extract produced antihyperglycemic effects in experimental diabetes.</td>
</tr>
<tr>
<td>Elgazar et al.24</td>
<td>Insulin resistance</td>
<td>Alloxan</td>
<td>Saffron extract</td>
<td>200, 400, 600</td>
<td>Oral</td>
<td>Rat</td>
<td>Saffron extract reduced blood glucose level and the incidence of different complications as results of hyperglycemia.</td>
</tr>
<tr>
<td>Kianhakht et al.25</td>
<td>Insulin resistance</td>
<td>Alloxan</td>
<td>(1) Saffron methanolic extract</td>
<td>1) 80 and 240</td>
<td>IP</td>
<td>Rat</td>
<td>Saffron methanolic extract, crocin and safranal significantly reduced the fasting blood glucose and HbA1c levels but significantly increased the blood insulin levels.</td>
</tr>
<tr>
<td>Arasteh et al.26</td>
<td>Insulin resistance, dyslipidemia</td>
<td>None</td>
<td>Saffron extract</td>
<td>50</td>
<td>IP</td>
<td>Rat</td>
<td>Hydromethanolic extract of saffron significantly decreased serum glucose and cholesterol levels and increased serum insulin.</td>
</tr>
<tr>
<td>Nasir et al.11</td>
<td>Hypertension</td>
<td>L-NAME</td>
<td>Saffron extract</td>
<td>200</td>
<td>Oral</td>
<td>Rat</td>
<td>Dietary saffron prevented blood pressure increases and remodeling of the aorta in hypertensive rats.</td>
</tr>
<tr>
<td>Imenshahidi et al.35</td>
<td>Hypertension</td>
<td>DOCA-salt</td>
<td>Saffron aqueous extract</td>
<td>10, 20, and 40</td>
<td>IP</td>
<td>Rat</td>
<td>Chronic administration of saffron aqueous extract reduced the mean systolic blood pressure in DOCA salt treated rats in a dose dependent manner.</td>
</tr>
<tr>
<td>Imenshahidi et al.36</td>
<td>Hypertension</td>
<td>DOCA-salt</td>
<td>Safranal</td>
<td>1, 2, and 4</td>
<td>IP</td>
<td>Rat</td>
<td>Chronic administration of safranal reduced the mean systolic blood pressure in DOCA salt treated rats in a dose dependent manner.</td>
</tr>
<tr>
<td>Imenshahidi et al.37</td>
<td>Hypertension</td>
<td>DOCA-salt</td>
<td>(1) Crocin</td>
<td>(1) 50, 100, and 200</td>
<td>IV</td>
<td>Rat</td>
<td>The aqueous extract of saffron stigma, safranal and crocin reduced the mean systolic blood pressure in normotensive and hypertensive anaesthetized rats in a dose-dependent manner.</td>
</tr>
<tr>
<td>Boskabady et al.38</td>
<td>Hypertension</td>
<td>DOCA-salt</td>
<td>Crocin</td>
<td>50, 100, and 200</td>
<td>IP</td>
<td>Rat</td>
<td>Chronic administration of crocin reduced the mean systolic blood pressure in DOCA salt treated rats in a dose dependent manner.</td>
</tr>
<tr>
<td>Higashino et al.42</td>
<td>Hypertension</td>
<td>None</td>
<td>Crocetin</td>
<td>25 and 50</td>
<td>Oral</td>
<td>Rat</td>
<td>Crocetin exert antihypertensive and antithrombotic effects via an increase in bioavailable nitric oxide.</td>
</tr>
<tr>
<td>Mashmoul et al.50</td>
<td>Obesity, dyslipidemia</td>
<td>High-fat diet</td>
<td>Saffron extract</td>
<td>1) 40 and 80 and 200</td>
<td>Oral</td>
<td>Rat</td>
<td>Crocin showed a higher antihyperglycemia activity compared with ethanolic extract of saffron but overall lower in comparison to orlistat. Moreover, crocin significantly reduced plasma levels of TG and TC while saffron extract showed major improvement in LDL/HDL level.</td>
</tr>
<tr>
<td>Hoshyar et al.51</td>
<td>Obesity, dyslipidemia</td>
<td>High-fat diet</td>
<td>(1) Saffron stigma</td>
<td>(1) 40</td>
<td>Oral</td>
<td>Rat</td>
<td>Saffron stigma, petal, and their mixture markedly decreased body weight and leptin levels as well as TC, TG, and LDL-C, and increased HDL-C in all experimental groups.</td>
</tr>
<tr>
<td>Kianhakht et al.52</td>
<td>Obesity</td>
<td>None</td>
<td>Saffron ethanolic extract</td>
<td>(1) 25, 50, 100, and 200</td>
<td>Gavage</td>
<td>Rat</td>
<td>Saffron extract and crocin at all doses significantly reduced body weight, food intake and leptin levels.</td>
</tr>
</tbody>
</table>
population suffer from MetS.\textsuperscript{16} MetS confers a 2-fold increase in the risk of cardiovascular diseases (CVD) and a 5-fold risk of developing type 2 diabetes mellitus (T2DM) over the next 5 to 10 years.\textsuperscript{17} It is also reported that patients with MetS are at a 2-fold higher risk of dying from stroke or myocardial infarction (MI) compared with those without the syndrome.\textsuperscript{18} Thus, MetS constitutes a major challenge for public health and it is quite necessary to identify and manage patients with MetS.\textsuperscript{19} Since there is no recognized method to prevent or improve the whole syndrome, the clinical management of patients with MetS is difficult. For these reasons, there is a particular interest nowadays in the potential of functional foods to modify the components of MetS.\textsuperscript{19,20} This review summarizes evidence that saffron and its active constituents can be considered as a potential dietary agent for prevention and treatment of MetS.

### EFFECT OF SAFFRON AND ITS ACTIVE CONSTITUENTS ON COMPONENTS ON METS

#### Insulin resistance.

The antidiabetic, hypoglycemic, and pancreas-protective effects of saffron and its active constituents have been investigated by several authors in chemically induced diabetic rats.\textsuperscript{21–25} Samarghandian et al. observed that saffron at 40 and 80 mg/kg significantly decreases blood glucose levels, glycosylated serum proteins, and serum advanced glycation end-products (AGEs) levels in streptozotocin (STZ)-induced type 2 diabetic rats.\textsuperscript{26} Similarly, Rajaei et al. found that crocin at a dose of 60 mg/kg significantly reduces the blood glucose level in STZ-induced diabetic animals.\textsuperscript{22} In another study, treatment of alloxanized mild diabetic (MD) and severely diabetic (SD) rats with saffron ethanolic extract at doses of 20, 40, and 80 mg/kg for 14 days significantly reduced fasting blood glucose (FBG) levels while increasing serum insulin level in these animals. The number of immunoreactive \( \beta \)-cells in the pancreas of extract-treated diabetic rats was also significantly increased.\textsuperscript{23} Elgazar et al. reported that oral administration of saffron extract induces a significant increase in serum insulin levels and a decrease in blood glucose levels in all treated alloxan-induced diabetic groups, compared to the control group.\textsuperscript{24} In another animal model of alloxan-induced diabetes, saffron methanolic extract (80 and 240 mg/kg), crocin (50 and 150 mg/kg), and safranal (0.25 and 0.5 mL/kg) reduce the FBG and glycated hemoglobin, HbA1\textsubscript{1c} levels in diabetic rats.\textsuperscript{25} Consistent with these findings, intraperitoneal administration of 50 mg/kg saffron extract decreases serum glucose levels and increases serum insulin levels, respectively, in healthy male rats.\textsuperscript{26}

It has been shown that saffron and its constituents elicit antidiabetic and hypoglycemic effects by (1) regulating the expression of adiponectin, tumor necrosis factor (TNF)-\( \alpha \), and leptin in white adipose tissue,\textsuperscript{27} (2) stimulating glucose uptake and increasing insulin sensitivity in skeletal muscle cells through both insulin-dependent [Phosphatidylinositol 3-kinase/AKT and mTOR] and insulin-independent [AMP-activated protein kinase (AMPK)/acetyl-CoA carboxylase (ACC) and mitogen-activated protein kinases (MAPKs)] pathways,\textsuperscript{14} (3) stimulating insulin release and increasing the expression of glucose transporter 4 (GLUT4) and AMPK,\textsuperscript{28} (4) increasing the number of immunoreactive \( \beta \)-cells in the pancreas,\textsuperscript{25} and (5) inhibiting protein tyrosine phosphatase 1B (PTP1B), a negative regulator of insulin signaling.\textsuperscript{29}

There are several studies indicating that not only diabetes but also diabetes-induced complications such as cardiovascular disease,\textsuperscript{30,31} liver disease,\textsuperscript{32} neuropathy,\textsuperscript{33} and nephropathy,\textsuperscript{34} can be ameliorated by saffron and its constituents. For example,
it was observed that saffron extract (5 and 25 mg/mL), crocin (10 and 50 μM), and γ-glutamylcysteinylglycine (GSH) (10 μM) decrease glucose-induced neurotoxicity and can be potentially useful in diabetic neuropathy treatment.33 Moreover, Altinoz et al. showed that treatment of diabetic rats with crocin decreases the high level of serum creatinine (Cr) and blood urea nitrogen (BUN) and markedly reduces the histopathological changes observed in the diabetes mellitus (DM) group.34 Therefore, saffron can be considered as a therapeutic agent in treating diabetes and diabetes-induced complications.

Hypertension. There are several studies which confirm the antihypertensive effects of saffron and its constituents in chemically induced hypertensive rats.11,35–38 Nasiri et al. investigated the effects of saffron stigma hydroalcoholic extract on blood pressure and the histology of the aorta in normotensive and NG-nitro-L-arginine methyl ester (L-NAME)-induced hypertensive rats. Results clearly showed that saffron decreases blood pressure elevation in hypertensive rats. They also found that the media thickness and elastic lamellae number of the aorta are also reduced by saffron treatment.11 Moreover, Imenshahidi et al. evaluated the effects of three doses of saffron aqueous extract on the blood pressure of normotensive and deoxycorticosterone acetate (DOCA)-salt-induced hypertensive rats. The authors found that chronic administration of saffron aqueous extract can reduce the mean systolic blood pressure (MSBP) in DOCA salt treated rats in a dose dependent manner, but it had no effect on the MSBP in normotensive rats.35 Consistent with the antihypertensive effects of saffron constituents, safranal and crocin also exhibited antihypertensive and normalizing effects on blood pressure.36,38 Furthermore, the intravenous administration of three doses of aqueous extract (2.5, 5, and 10 mg/kg), crocin (50, 100, and 200 mg/kg), and safranal (0.25, 0.5, and 1 mg/kg) reduced the mean arterial blood pressure (MABP) in normotensive and DOCA-induced hypertensive rats in a dose-dependent manner. The authors concluded that the hypotensive properties of saffron can be attributable, in part, to the actions of two major constituents of this spice, crocin and safranal. Further studies showed that safranal is more effective than crocin in lowering blood pressure in rats.37 The exact mechanisms of the hypotensive effect of these compounds are not yet known, but it can be partly attributed to the potent relaxant effect of saffron and safranal on smooth muscle cells.39 Moreover, Hoseinzadeh et al. showed that safranal regulates GABA(A)-benzodiazepine receptor complex.40 It has been shown that benzodiazepines, in preanesthetic doses, induces hypotension by decreasing peripheral resistance or cardiac output.41 Furthermore, Higashino et al. examined the effects of crocetin in stroke-prone spontaneously hypertensive rats (SHRSPs). Results showed that crocetin significantly inhibits the age-related increase in systolic blood pressures in SHRSPs at 25 and 50 mg/kg/day.42

It has been shown that crocin and crocin differentially affect vascular contractility and activate different mechanisms involved in the vasoconstriction pathway in hypertension. Llorens et al. reported that crocetin exerts prorelaxing actions through endothelial cells which are partially dependent on nitric oxide (NO), while crocin has pro-contractile effects on smooth muscle cells.43 However, the contractile effects of crocin observed in this study are in contrast to vasodilatory effects observed in other studies.43,44 The precise mechanisms of antihypertensive and vasomodulatory effects of saffron and its constituents are not yet clear. For instance, it has been shown that saffron and its constituents increase the levels of antioxidant NO by enhancing endothelial NO synthase (eNOS) activity.42,35–47 Moreover, these molecules elicit vasorelaxing functions on smooth muscle cells via blocking of calcium channels48 or inhibiting sarcoplasmic reticulum Ca2+ release into the cytosol.49 Understanding these mechanisms can lead to the development of new strategies to advance therapeutic procedures for hypertension-related complications including MetS.

Obesity. The antiobesity and weight-loss promoting effects of saffron and its constituents have been reported in several studies.15,50,51 In a study by Mashmoul et al., the 8-week treatment with crocin (80 mg/kg) significantly decreases the rate of body weight gain, total fat pad, and weight ratio of epididymal fat to body in obese rats that were on a high fat diet (HFD) for 12 weeks. Moreover, treatment with saffron extracts (40 and 80 mg/kg) significantly reduces food consumption in rats.50 In another study, treatment of high-fat-fed obese rats with different concentrations of saffron stigma, petal, and their mixture for 3 weeks significantly decreased body weight and leptin levels in all experimental groups.51 Moreover, Kianbakht et al. reported that daily gavage of saffron methanolic extract (25, 50, 100, 200 mg/kg) and its active constituent crocin (5, 15, 30, 50 mg/kg) to obese rats for 2 months reduces body weight, food intake, and leptin levels.52 Decrease in leptin levels is at least partially due to the reduction of fat mass, since leptin is a hormone secreted by adipose tissue and adipocytes.52 In a randomized, placebo-controlled study on 60 healthy, mildly overweight women, supplementation with Satiereal (176.5 mg per day), a novel extract of saffron stigma, potentiated body weight reduction after 8 weeks of treatment.53 Moreover, Gout et al. reported a significant decrease in mean snacking frequency among Satiereal group as compared with the placebo group.53 Consistently, examining the antidepressant effects of saffron on major depressive disorder, a meta-analysis of five randomized clinical trials (two placebo-controlled trials and three antidepressant-controlled trials) showed that appetite reduction is one of the most frequent reported adverse effects of saffron supplementation.54

In an in vivo study using a rat model, crocin showed several antiobesity mechanisms similar to those of orlistat.13 The results of the in situ loop method as well as enzyme assay showed that crocin could selectively inhibit the activity of pancreatic and gastric lipases as a competitive inhibitor. However, there are some differences between the inhibitory functions of crocin with orlistat. For instance, (1) orlistat reduces the dietary fat absorption more effectively than crocin. Orlistat reduces the dietary fat absorption by approximately 30% at a dose of 40 μmol/kg,55 but crocin reduces the dietary fat absorption by 12% at a dose of 102 μmol/kg. (2) The inhibitory effect of orlistat on lipase is irreversible, whereas crocin inhibits the lipase reversibly, since no covalent modification of lipase by crocin occurs.56 (3) Orlistat strongly inhibits both pancreatic and gastric lipases, but crocin has a more potent inhibitory effect on pancreatic lipase. (4) The other difference is that although crocin is not absorbable, orlistat can be minimally absorbed and consequently leads to hepatotoxicity.56 And (5) finally, orlistat has some adverse gastrointestinal effects including fatty/oily stool, fecal urgency, diarrhea, system flatulence, and abdominal pain,57 whereas these side effects are not observed following crocin treatment. In agreement with this result, a 1-month randomized double-
Review

suggested to be inversely related to central adiposity.59 Therefore, considering these protective functions of saffron, its active constituents may be considered as a promising natural medicine in the treatment of obesity.

Dyslipidemia. There are studies supporting the role of saffron and its active constituents in modulating serum total cholesterol (TC), total triglyceride, low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C).21,26,51,60 For instance, in a study investigating the protective effects of saffron in streptozotocin (STZ)-induced type 2 diabetic rats, saffron at 40 and 80 mg/kg significantly increases HDL-C, whereas it decreases cholesterol, triglyceride, and LDL-C after 28 days of treatment.21 Similar to these findings, Arasteh et al. reported that intraperitoneal administration of 50 mg/kg saffron extract significantly decreases levels of cholesterol in healthy male rats.26 To further support the protective functions of saffron on dyslipidemia, Hoshyar et al. investigated the effects of extracts from saffron stigmas, petals, and their mixture on dyslipidemia. Results showed that saffron extracts markedly decrease the serum total cholesterol, triglyceride, and LDL-C in obese rats, while HDL-C is increased.54 Furthermore, in another study by Mashmoul et al., the saffron extracts and crocin were fed to rats by mixing with a high fat diet for 8 weeks. The authors reported that crocin (80 mg/kg) significantly reduces the plasma levels of triglyceride and TC while the saffron extract (40 mg/kg) showed major improvement in LDL/HDL level.50 Consistent with these results, Shirali et al. showed that intraperitoneal injection of crocin at doses of 50 or 100 mg/kg significantly decreases the levels of serum triglyceride, TC, and LDL-C and increases the HDL-C in the STZ-induced diabetic rats.60 Moreover, Sheng et al. reported that a 10-day treatment of diet-induced hyperlipidemic rats with crocin in a daily dose range of 25 to 100 mg/kg can significantly reduce serum triglyceride, TC, LDL-C and very low density lipoprotein cholesterol (VLDL-C) levels.13 To further support the protective role of saffron on dyslipidemia, He et al. also reported that crocin has a potent hypotriglycerideremic and hypocholesterolemic activity in atherosclerotic quails.13 Moreover, Asdaq et al. showed that the antihyperlipidemic and antioxidant function of saffron is more effective than crocin, suggesting the presence of other constituents other than crocin in saffron extracts with antioxidant and hypolipidemic properties.64

Several mechanisms have been proposed to explain the hypolipidemic effects of saffron extract and its constituents including (1) inhibitory effect on pancreatic and gastric lipases as a competitive inhibitor,15 (2) stimulating effects on serum adiponectin levels,51,62 and (3) modulatory effects on the oxidant-antioxidant system.63 Therefore, considering these potent antihyperlipidemic and antioxidant effects, saffron can be considered as a promising agent in treating dyslipidemia.

■ CONCLUSION

Recently, saffron attracted attention in the management of MetS complications and provides a new research area for therapy purposes. There are studies showing that saffron and its major bioactive components including crocin, crocetin, and safanal could ameliorate MetS symptoms in both animal and clinical studies. In line with the above-mentioned findings, 66 patients diagnosed with schizophrenia who were on olanzapine treatment were randomly allocated to receive a capsule of saffron aqueous extract (30 mg/day), crocin (30 mg/day), or placebo in a 12-week triple-blind trial. The results showed that saffron aqueous extract and, to some extent, crocin could effectively prevent reaching the criteria of MetS in schizophrenic patients who were treated with olanzapine.64 Furthermore, saffron and its active constituents have also shown anti-inflammatory effects in subjects with MetS.65,66 In a study conducted by Kermani et al., forty-four adults diagnosed with MetS were randomly divided into 2 groups, to receive 100 mg/day saffron for 12 weeks. The authors reported that saffron is able to modulate the serum concentrations of several pro-inflammatory and anti-inflammatory cytokines such as vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), and epidermal growth factor (EGF).65 In another study, 8-week supplementation with crocin reduced serum anti-hsp27 titers by 13% in patients with MetS.66 This review summarizes the recent findings on the protective roles of saffron in the pathogenesis of MetS (Figure 2).

Figure 2. Schematic representation of saffron-mediated protective responses in MetS pathology. Saffron attenuates MetS complications including hypertension, hyperglycemia, obesity, and dyslipidemia.

The precise mechanisms of the protective functions of saffron and its constituents on MetS constituents are not yet clear. Better understanding of these regulatory mechanisms can lead to the development of new strategies to advance therapeutic procedures for this disease. It is well-known that signaling functions of herbal extracts are complex and paradoxical in some cases. It is recommended that further investigation be performed in this regard in order to determine the exact mechanism of saffron and its components in combination with other standard therapeutic approaches on MetS patients. Furthermore, it is not yet clearly understood whether these beneficial effects are attributable to crocin, crocetin, picrocrocin, safranal or a combination of these active ingredients. Understanding of the molecular mechanisms involved in saffron protective properties as well as identifying the active components responsible for these protective effects could therefore help to design novel active molecules and potentially new drugs to regulate pathological responses and have a great clinical significance in terms of the treatment of MetS complications.
AUTHOR INFORMATION

Corresponding Authors
*Seyed Mahdi Hassanian, Ph.D., Department of Medical Biochemistry Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Phone: (+98) 5138002375, Fax: (+98) 5138002389, E-mail: hasanianmehrm@mums.ac.ir.
*Majid Khazaei, MD, Ph.D., Department of Medical Physiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Phone: (+98) 5138002227, Fax: (+98) 5138002389, E-mail: KhazaeiM@mums.ac.ir.

ORCID

Seyed Mahdi Hassanian: 0000-0002-5247-4043

Author Contributions
△M.S., N.S.A.M., M.N., M.T., and A.A. made equal contributions to this study.

Funding

This study was supported by grants awarded by the Mashhad University of Medical Sciences (Grant No. 951824) and National Institute for Medical Research Development (Grant No. 958349).

REFERENCES

(33) Mousavi, S. H.; Tayarani, N. Z.; Parsaei, H. Protective effect of saffron extract and crocin on reactive oxygen species-mediated high


