Chapter 29

Cardiovascular effects of saffron and its active constituents

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Chapter Outline

29.1 Introduction

Saffron (*Crocus sativus* L.) is used as a coloring and flavoring agent in food preparation as well as in perfumes and cosmetics (Alavizadeh and Hosseinzadeh, 2014; Mollazadeh et al., 2015). The main components of saffron stigmas are carotenoids (crocetin, crocins, α-carotene, lycopene, zeaxanthin), monoterpene aldehydes (picrocrocin and safranal), monoterpenoids (crocusatines), isophorones, and flavonoids. Crocins and crocetin are saffron coloring agents, while the unique aroma of saffron is related to safranal (Hosseinzadeh and Nassiri-Asl, 2013). Additionally, saffron has been employed for many purposes in traditional medicine, and therefore the pharmacological activities of saffron and its constituents have been extensively studied. These include antioxidant (Hosseinzadeh et al., 2009b), antinociceptive (Amin and Hosseinzadeh, 2012; Amin et al., 2017), antiinflammatory (Hosseinzadeh and Younesi, 2002), antidepressant (Ghasemi et al., 2015; Hosseinzadeh et al., 2004, 2007; Vahdati-Hassani et al., 2014), anxiolytic (Hosseinzadeh and Noraei, 2009), anticonvulsive (Sadeghnia et al., 2008), antitussive (Hosseinzadeh and Ghenaati, 2006), antiischemic (Hosseinzadeh et al., 2009a), anti-Alzheimer's (Hosseinzadeh and Ziaei, 2006; Hosseinzadeh et al., 2012), antigenotoxic (Hosseinzadeh et al., 2007a), and anticancer activities (Rastgoo et al., 2013). Saffron also functions as an antidote to various toxic insults (Razavi and Hosseinzadeh, 2015) and exhibits hypolipidemic (Sheng et al., 2006) effects. Accumulating evidence supports protective effects of saffron and its active components in different organs such as the brain (Dorri et al., 2015; Kamyar et al., 2016; Mehri et al., 2012), heart (Razavi et al., 2013a), kidney (Amin et al., 2015), liver (Lari et al., 2014, 2015), gastrointestinal tract (Khorasany and Hosseinzadeh, 2016), and immune system (Khajuria et al., 2010). Saffron is also able to manage metabolic syndrome (Razavi and Hosseinzadeh, 2017). Because of its safety (Bostan et al., 2017), unique antioxidant and antiinflammatory properties, and ability to decrease lipid levels, saffron may be one of the best supplements for cardiac health. In Mediterranean countries the incidence of heart disease is lower than other countries, possibly due to the common use of saffron (Kamalipour and Akhondzadeh, 2011). Saffron is found to reduce the risk of cardiovascular disorders such as arrhythmia, ischemic reperfusion, hypertrophy, hypertension, and atherosclerosis (Fig. 29.1). In this chapter, we summarize various studies related to the effects of saffron and its main constituents on the cardiovascular system.

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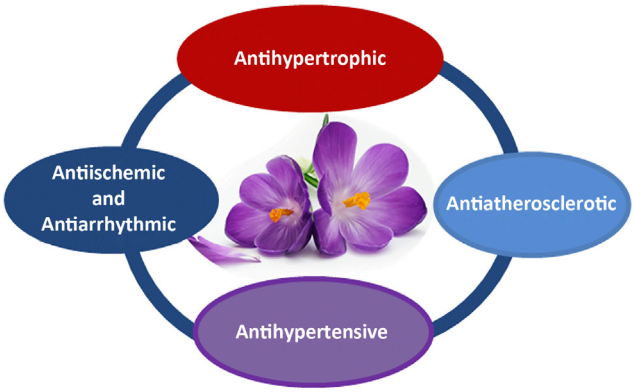

FIGURE 29.1 Schematic description of the effects of saffron and its main constituents on the cardiovascular system.

29.2 Cardiovascular pharmacological effects of saffron

29.2.1 Antiarrhythmic and antiischemic effects

Antiarrhythmic effects of saffron have been identified in several studies. The effects of aqueous ethanolic extract of saffron on heart rate and contractility were evaluated on isolated guinea pig hearts. Significant reductions in heart rate and contractility were observed. The suppressive effects of the extract on guinea pig heart rate and contractility may be due to a potent inhibitory effect on calcium channels (Boskabady et al., 2008). In another study on isolated, perfused atrioventricular (AV) nodes of rabbits, saffron protected AV nodes from supraventricular arrhythmia. According to the results of this study, saffron nonspecifically affected the transitional cells of the fast nodal pathway through a rate-independent increase in basic and functional (facilitation and fatigue) parameters of the AV node (Khori et al., 2006.). In addition, the findings of another study suggested that saffron has no toxic effects on cardiac autonomic nervous system activity. Moreover, the stability of heart sympathovagal balance may be improved by saffron in normal rats (Joukar and Dehesh, 2015).

Myocardial ischemia is defined as the reduction of blood flow to cardiac muscle as a result of partial or complete blockade of the coronary arteries. Although reperfusion is considered a recovery process for the ischemic myocardium, it often induces damage to the reperfused tissue because of the increased generation of reactive oxygen species (ROS) (Zhou et al., 2015). Saffron was found in several investigations to attenuate ischemia-reperfusion (IR) injuries because of its antioxidant effects. For instance, oral administration of saffron for 6 weeks improved left ventricle pressure, heart rate, coronary flow, and left ventricle end diastolic pressure. Results also indicated that saffron reduced infarct size, lowered lipid peroxidation, and increased glutathione peroxidase (GPX) activity. Furthermore, saffron restored the decreased level of phosphorylated Akt and 4EBP1 and reduced the level of p38 compared to IR hearts (Nader et al., 2016).

Another study indicated that crocin [20 mg kg^{-1} day^{-1}, intraperitoneally (IP), for 21 days] improved reperfusion-induced arrhythmias. Data showed IR injury significantly reduced superoxide dismutase (SOD) activity and glutathion (GSH) content and elevated malondealdehyde (MDA) levels in heart muscle. Crocin significantly increased catalase activity in heart tissue compared to the IR group due to its antioxidant activity. The use of crocin for treatment or prevention of arrhythmias in patients with ischemic heart disease was suggested in this study (Jahanbakhsh et al., 2012). In a similar study, treatment with saffron extract (100 mg kg^{-1} day^{-1}, orally) for 7 days prior to IR injury reduced the susceptibility and occurrence of lethal ventricular arrhythmia during the reperfusion. This protection may be attributed to a decrease in electrical conductivity and prolonged duration of the action potential (Joukar et al., 2013).

As cardiac IR is associated with oxidative injury, another study compared the protective effects of crocin (40 mg kg^{-1}, orally for 21 days) and vitamin E during IR. Results in an isolated rat heart model indicated that crocin exhibited the same protective effect as vitamin E against cardiac IR injury by elevation of total antioxidant capacity (Dianat et al., 2014a,b). In addition to crocin, safranal is also able to protect against IR injury. To demonstrate this, safranal (0.1−0.5 mL kg^{-1} day^{-1}, IP) was administrated to rats for 14 days, and on day 15 one-stage ligation of the left anterior descending coronary artery was performed for 45 minutes followed by 60-minute reperfusion. Safranal reduced infarct size, improved left ventricular functions, and modulated hemodynamic heart parameters. The probable mechanism of safranal protection is increased phosphorylation of Akt/glycogen synthase kinase-3b/eNOS pathway and decreased IKK-b/NFκB protein expression in heart tissue. Moreover, safranal increased the levels of myocardial

antioxidant and decreased the level of nitrotyrosine. The increased level of creatine kinase MB (CK-MB) and decreased level of lactate dehydrogenase (LDH) in IR heart, were normalized in safranal pretreated rats. Safranal reduced tumor necrosis factor-α (TNF-α) levels in IR heart in a dose-dependent manner. Safranal also protected myocardial architecture and reduced inflammatory cell numbers and edema (Bharti et al., 2011).

29.2.2 Protective effects against cardiac hypertrophy

Cardiac hypertrophy, an independent risk factor of cardiovascular disease, is an important cause of morbidity and mortality worldwide. Prolonged compensatory adaptation of cardiac hypertrophy leads to worsening myocardium, both functionally and histologically. It has been suggested that cardiac hypertrophy and cardiac failure are induced by mechanical left ventricular wall stress as a result of induction of ROS (Das et al., 2004).

It has been demonstrated that crocetin (25 and 50 mg kg^{-1}, IP, for 15 days) prevented cardiac hypertrophy induced by norephinephrine (NE) through inhibition of lipid peroxidation and increased the activity of antioxidant enzymes such as SOD and GPX. An additional study showed that crocetin significantly repaired myocardial damages induced by NE. Results indicated that the antioxidative effects of crocetin were stronger than those of captopril (the positive control); however, the effect of crocetin on improving cardiac hypertrophy, particularly on the left ventricular index, was less than captopril (Shen and Qian, 2006). Results of another study by Shen et al. (2006) showed crocetin increased both cardiac Na^+ K^+ ATPase and mitochondrial Ca^{2+} Mg^{2+} ATPase activity and significantly inhibited the activity of matrix metalloproteinase-2 (MMP-2) as well as MMP-2 and MMP-9 mRNA expression. In primary culture of cardiac myocytes exposed to noradrenaline, crocetin significantly reduced the activity of LDH and elevated mitochondrial succinic dehydrogenase activity, ATPase (Na^+ K^+ ATPase and Ca^{2+} ATPase) activity, and mitochondrial membrane potential. Therefore crocetin suppressed the impairment of energy metabolism and attenuated the induction of apoptosis in cardiac myocytes exposed to noradrenaline (Shen et al., 2004).

Another study showed that crocetin (1−10 μM) inhibited cardiac hypertrophy induced by angiotensin II (Ag II) in cultures of primary cardiac myocytes and fibroblasts in a dose-dependent manner. Moreover, crocetin (50 mg kg^{-1} day^{-1}) protected and reversed cardiac hypertrophy induced by aortic banding in vivo. According to this study, crocetin not only prevented the development of cardiac hypertrophy but also reversed established cardiac hypertrophy by inhibiting hypertrophy, inflammation, and fibrosis dependent on ROS and the MEK-ERK1/2 kinase pathway. Thus the MEK-ERK1/2 pathway is a target of the inhibitory effects of crocetin (Cai et al., 2009).

Furthermore, in a rat model of cardiac hypertrophy induced by overloading pressure, crocetin (50 and 100 mg kg^{-1}, gavage, for 30 days) reduced the cardiac indexes and hydroxyproline content in the heart, increased the activity of Na^+ K^+ ATPase and Ca^{2+} Mg^{2+} ATPase, as well as attenuated the activity of MMPs (Shen and Qian, 2004).

29.2.3 Effects of saffron and its active constituents on blood pressure

Antihypertensive effects of saffron and its main constituents have been shown in both acute and chronic administration during both animal and clinical studies. Mechanisms including the blocking of calcium channels, inhibition of sarcoplasmic reticulum Ca^{2+} release into the cytosol, interaction with endothelial nitric oxide (NO), and antioxidant activity may be involved in hypotension induced by saffron. According to the study by Razavi et al. (2016a), an endothelium independent mechanism may also be involved in vasodilatory and hypotensive effects of safranal.

Aqueous and ethanolic extracts of saffron petals were shown to reduce mean arterial blood pressure (BP) in anaesthetized rats in a dose-dependent manner and to inhibit contractile responses produced by electrical field stimulation of isolated rat vas deferens and guinea pig ileum (Fatehi et al., 2003). In addition, dose-dependent hypotensive effects of intravenous injection of aqueous extract of saffron stigma (2.5, 5, and 10 mg kg^{-1}) and its two active constitutes have been demonstrated in normotensive and hypertensive anaesthetized rats. As reflex tachycardia was not observed in this study, it could be suggested that both heart function and blood vessel contractility are affected by saffron. The effect of safranal on lowering BP was greater than that of other saffron components. Crocin significantly reduced BP in hypertensive anaesthetized rats (Imenshahidi et al., 2010).

Other studies indicated that chronic administration of saffron aqueous extract, crocin, or safranal could reduce the mean systolic BP in deoxycorticosterone acetate salt-treated rats. The results also showed that the antihypertensive effects of these agents did not persist (Imenshahidi et al., 2013, 2014, 2015). Oral treatment with hydroalcoholic extract of saffron (200 mg kg day^{-1}) for 5 weeks reduced BP in rats with hypertension induced by NG-nitro-L-arginine methyl ester in drinking water and decreased the cross section area, median thickness, and elastic lamellae number of the aorta (Nasiri et al., 2015). The vasomodulatory effects of crocetin in hypertension has been established in another study,

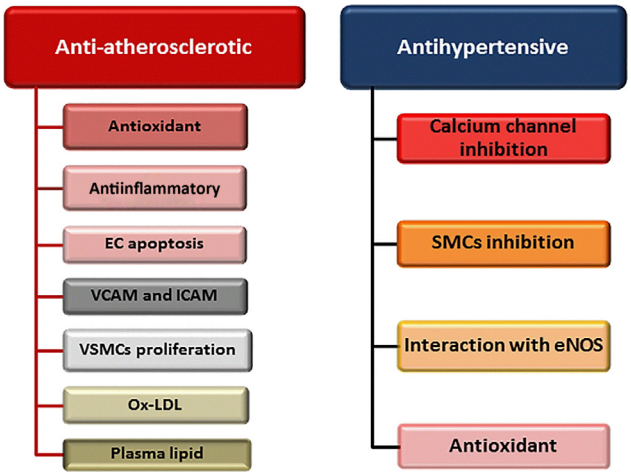

FIGURE 29.2 Different mechanisms of antiatherosclerotic and antihypertensive effects of saffron.
EC, Endothelial cell; *ICAM*, intercellular adhesion molecule; *Ox-LDL*, oxidized LDL; *VCAM*, vascular cell adhesion molecule; *VSMCs*, vascular smooth muscle cells.

which indicated crocetin improved endothelium-dependent acetylcholine relaxations through endothelial NO but not the cyclooxygenase pathway (Mancini et al., 2014) (Fig. 29.2).

In a double-blind, placebo-controlled randomized study on 260 infertile men, treatment with saffron (60 mg day^{-1} for 26 weeks) caused an 11.8% decrease in mean systolic BP and a 10.8% decrease in mean diastolic BP (Safarinejad et al., 2011). In another double-blind, placebo-controlled study in healthy adult volunteers, saffron tablets (400 mg day^{-1} for 1 week) significantly reduced standing systolic BP and mean arterial pressure (Modaghegh et al., 2008).

29.2.4 Antiatherosclerotic effects of saffron and its active constituents

Antiatherosclerotic effects of saffron and its main components have been evaluated in different studies. Due to antioxidant and inhibitory effects on endothelial cell apoptosis, atherosclerosis can be prevented by saffron. In vitro studies indicated that crocin increased intracellular calcium induced by H_2O_2 in bovine aortic endothelial cells (BAECs) due to antioxidant and antiapoptotic effects by downregulating the increased level of Bax/bcl2 (He et al., 2004; Xu et al., 2006). Endothelial dysfunction is involved in the initiation and progression of atherosclerosis. In one study, endothelial dysfunction was induced in both in vivo and in vitro experiments. In vivo, feeding of a high cholesterol diet to rabbits and in vitro treatment of BAECs with oxidized LDL (ox-LDL) were used. Results showed that crocetin significantly improved the endothelium-dependent relaxation of the thoracic aorta in hypercholesterolemic rabbits through increased aortic endothelial nitric oxide synthase (eNOS) activity, which led to elevation of NO production (Tang et al., 2006). In another experiment, crocetin protected advanced glycation end products (AGEs)-induced bovine endothelial cell apoptosis and adhesion of leukocytes to endothelial cells. This effect occurred through ROS inhibition, intracellular calcium stabilization, and downregulation of the expression of intercellular adhesion molecule-1 (ICAM-1), suggesting a beneficial effect of crocetin on prevention of diabetes-induced vascular complications (Xiang et al., 2006a,b). Similar results were observed during treatment with crocetin in human umbilical vein endothelial cells in which crocetin inhibited high glucose-induced apoptosis through the PI3K/Akt/eNOS pathway (Meng and Cui, 2008). In addition, the protective effects of crocetin against the migration and proliferation of vascular smooth muscle cells (VSMCs) induced by AGEs have been shown. Crocetin reduced the levels of TNF-α, IL-6, and MMP-2 and MMP-9. Considering these studies, it can be suggested that crocetin may have a beneficial effect in preventing diabetes-associated cardiovascular complications (Xiang et al., 2017).

VSMC proliferation plays a main role in the development and progression of atherosclerosis. A study showed that crocetin alleviated angiotensin II-induced VSMC proliferation, potentially in part due to its inhibition of ERK1/2 through a calcium-dependent pathway (Zhou et al., 2006, 2007) and inhibition of PKC activity (Zhou et al., 2010b). Inhibition of the cell cycle G1/S transition by crocetin in VSMC is mediated through suppression of cyclin D1 and elevation of p27kip1 (Zhou et al., 2010a).

Moreover, in another study crocin inhibited the proliferation of SMCs and formation of foam cells induced by ox-LDL in bovine aortic smooth muscle cells (BASMCs) in a concentration-dependent manner, which promoted the initiation and progression of atherosclerosis. Crocin also inhibited total cholesterol (TC) and cholesteryl ester accumulation induced by ox-LDL in macrophages. Crocin could also inhibit intracellular calcium elevation in SMC. It is suggested that crocin showed antiatherosclerotic effects via decreasing the level of ox-LDL, which has an important role in the initiation and progression of atherosclerosis. In addition, in ox-LDL and hyperlipidemic diet-induced atherosclerosis in quails, crocin could reduce MDA and increase NO in serum, decrease the level of serum TC, triglyceride (TG), low-density lipoprotein-cholesterol (LDL-C), and inhibit the formation of aortic plaques (He et al., 2005, 2007). Furthermore, in another study suppression of LDL oxidation by crocetin attenuated atherosclerosis in hyperlipidemic rabbits (Zheng et al., 2006).

The lipid lowering effect of saffron is considered another antiatherosclerotic mechanism. Different studies indicated saffron and its active constituents modulated serum TC, TG, LDL, and high-density lipoprotein (HDL). For example, a mixture of extracts from stigma and petal of saffron improved dyslipidemia in obese rats and reduced atherosclerosis. The atherosclerosis index (LDL/HDL) and atherogenic index (TC/HDL) were also improved after saffron treatment (Hoshyar et al., 2016). Another study conducted on rats that received a high fat diet for 12 weeks indicated that crocin (80 mg kg^{-1}) significantly reduced plasma levels of TG and TC, whereas saffron ethanolic extract (40 mg kg^{-1}) significantly improved their atherogenic index (the level of LDL/HDL) (Mashmoul et al., 2014). Moreover, a 10-day treatment with crocin (25−100 mg kg^{-1}) significantly reduced TG, TC, LDL-C, and very low-density lipoprotein-cholesterol (VLDL-C) in diet-induced hyperlipidemic rats through inhibition of pancreatic lipase, which leads to the malabsorption of fat and cholesterol (Sheng et al., 2006). Besides crocin, crocetin (25 and 50 mg kg^{-1} for 10 weeks) also reduced high cholesterol diet-induced dyslipidemia in rats, potentially due to antioxidant and antiinflammatory effects as well as downregulation of phosphorylated p38 MAPK (Diao et al., 2018).

In another study of hypercholesterolemia-induced atherosclerosis in rabbits, crocetin reduced NF-κB activation, resulting in suppressed expression of the adhesion molecule VCAM-1 (Zheng et al., 2005). In addition to antihyperlipidemic effects, a hydromethanolic extract of saffron exhibited hypolipidemic effects in healthy male rats. The hydromethanolic saffron extract (50 mg kg^{-1}, IP) significantly reduced serum TC levels in healthy male rats after 14 days of treatment (Arasteh et al., 2010).

It is well-known that adiponectin has an important role in the regulation of lipid metabolism. Reduced levels of adiponectin, a cytokine released from adipose tissue, are associated with hypertension, hyperlipidemia, diabetes, and atherosclerosis (Izadi et al., 2013). It was demonstrated that ethanolic and aqueous saffron extracts significantly increased adiponectin levels in streptozotocin (STZ) diabetic rats (Hemmati et al., 2015). It was also found that saffron can moderately stimulate peroxisome proliferator-activated receptor α (PPARα). PPARα activation has a role in lipid profile improvement and atherosclerosis (Duval et al., 2007). Thus another mechanism of saffron antiatherogenic effects could be PPARα activation. In a randomized, placebo-controlled clinical trial on patients with metabolic syndrome, the attenuating effect of saffron (100 mg day^{-1}) on serum heat shock protein (HSPs 27 and 70) antibody titers was demonstrated. Following exposure to stressful conditions such as several cardiovascular disease risk factors, the expression of HSPs was increased. According to the literature, there is a positive association between plasma antibody titers to HSPs and cardiovascular disease such as atherosclerosis (Shemshiana et al., 2014) (Fig. 29.2).

Inhibitory effects of saffron on platelet aggregation and coagulation have been shown in multiple studies. Saffron aqueous extract inhibited platelet aggregation induced by ADP, epinephrine, and collagen in human platelets (Jessie and Krishnakantha, 2005). The presence of both platelet aggregation inducer and inhibitor has been identified in bulbs of *C. sativus* var. Cartwrightianus (Liakopoulou-Kyriakides and Skubas, 1990). In contrast to the work discussed earlier, saffron tablets (200 and 400 mg kg^{-1}) ingested for 1 week had no effect on coagulant and anticoagulant systems (Ayatollahi et al., 2014) (Fig. 29.3).

29.2.5 Protective effects of saffron and its active constituents on natural and chemical toxins

The protective effects of saffron and its active constituents have been shown against some chemical and natural toxins including diazinon (an organophosphate insecticide), isoproterenol (a synthetic nonselective β adrenoceptor), doxorubicin (an antitumor agent), and patulin (a mycotoxin). It has been reported that diazinon (15 mg kg^{-1}, gavage, for 28 days) induced cardiovascular toxicity due to oxidative stress. In isolated rat aorta, crocin (20 mg kg^{-1}, IP, for 28 days) decreased toxic effects of diazinon through decreasing lipid peroxidation and improving impaired contractile and relaxant responses in rat aorta (Razavi et al., 2014). Moreover, the BP normalizing effect of crocin has been demonstrated in a study that indicated coadministration of crocin and diazinon restored the increase of systolic BP and decrease of heart

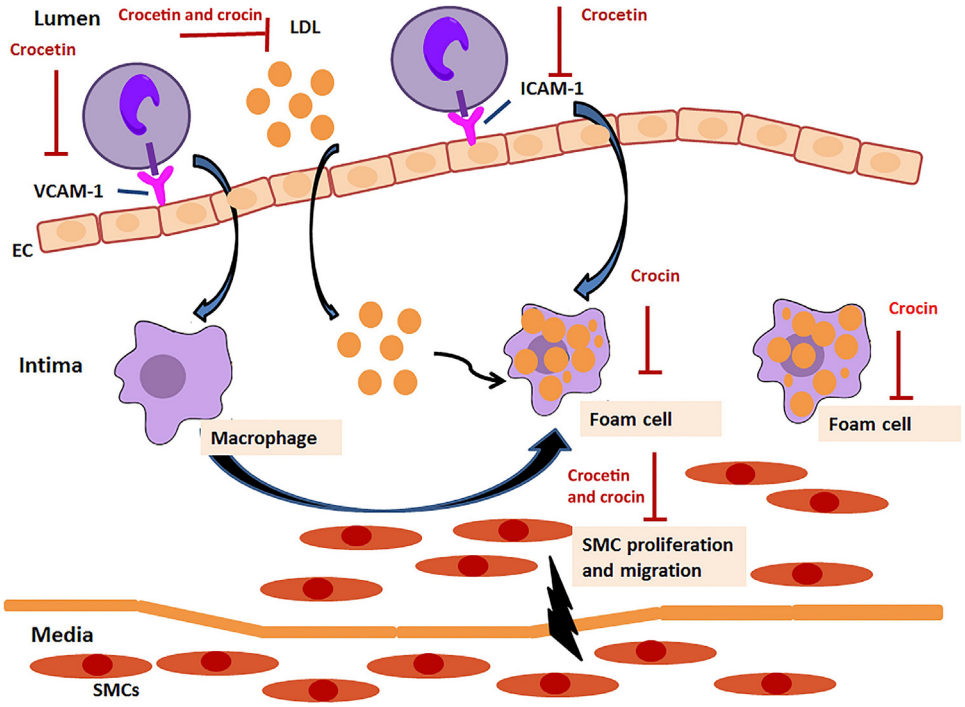

FIGURE 29.3 Schematic description of antiatherosclerotic mechanisms of saffron and its main constituents.
ICAM-1, Intercellular adhesion molecule-1; *SMC*, smooth muscle cell; *VCAM-1*, vascular cell adhesion molecule-1.

rate caused by subchronic diazinon administration in rats (Razavi et al., 2013b). In addition to antioxidant effects, other research has shown that diazinon-induced apoptosis by activation of caspase 9 and caspase 3 and via elevation of the Bax/Bcl2 ratio. Crocin inhibited apoptosis in aortic tissue (Razavi et al., 2016b).

Data obtained from in vivo studies revealed that crocin protected against diazinon-induced oxidative stress and mitochondrial-mediated apoptosis in heart tissue of rats after subchronic exposure (Razavi et al., 2013a). The increased level of CK-MB (a cardiac injury biomarker) due to diazinon exposure in rats was reduced following treatment by crocin, saffron aqueous extract, and safranal (Hariri et al., 2014; Razavi et al., 2013a).

Studies have evaluated the cardioprotective effect of extracts from saffron, crocin, and safranal in isoproterenol-induced myocardial infarction in rats. According to these studies, crocin (20 mg kg^{-1} day^{-1}, IP, for 21 days), saffron extract (20, 40, 80, and 160 mg kg^{-1}, IP) and safranal (0.025, 0.050, and 0.075 mL kg^{-1} IP) for 8 days, significantly reduced the LDH and CK-MB in serum and myocardial lipid peroxidation induced by isoproterenol. Moreover, histopathological examination showed that saffron and its active constituents restored myocardial injury induced by isoproterenol (Goyal et al., 2010; Mehdizadeh et al., 2013). In another study, oral administration of saffron (200, 400, and 800 mg kg^{-1}) for 4 weeks showed significant cardioprotective effects against isoproterenol-induced myocardial injury through stabilizing hemodynamics and left ventricular functions, restoring structural integrity, and enhancing antioxidant status. Saffron at 400 mg kg^{-1} showed maximum protective effects (Sachdeva et al., 2012).

In isolated rabbit hearts, ROS were generated by two models including electrolysis of the perfused heart solution and/or perfusion with 30 μM doxorubicin, both in the presence and absence of 10 μg mL^{-1} saffron extracts. Results indicated that ROS decreased ventricular pressure, heart rate, and coronary flow and elevated lipid peroxidation, whereas SOD activity decreased. ROS also induced myocardial architecture alteration. Perfusion with saffron during electrolysis decreased ROS and improved myocardial function. However, the effect of saffron against doxorubicin was less suggesting that mechanisms other than oxidative stress may be involved in doxorubicin cardiotoxicity (Chahine et al., 2013). In another study conducted by the same authors, doxorubicin increased ischemic tissue damage in isolated rabbit heart during 40 minutes of reperfusion. Saffron extract significantly decreased oxidative myocardial damage during the first minutes of reperfusion, but the effect was less than when given before ischemia. Saffron increased cardiac troponin T proteins, inhibited the p38 mitogen-activated protein kinases pathway, and activated the AKT/mTOR (mammalian target of rapamycin)/4EBP1 pathway in reperfusion and doxorubicin treated rabbit hearts (Chahine et al., 2014).

Crocin is able to protect the heart against toxicity induced by natural toxins such as patulin. Patulin is a mycotoxin produced principally by *Penicillium expansum* but also by several species of the genera of *Penicillium*, *Aspergillus*, and *Byssochlamys*. One study found that patulin induced cardiotoxicity by increasing the level of creatinin phosphokinase,

elevation of lipid and protein oxidation, induction of apoptosis through overexpression of P53, and activation of caspase 3. Crocin improved all toxic cardiac effects of patulin in mice (Boussabbeh et al., 2015).

29.3 Conclusion

This chapter suggests that saffron and its constituents including crocin, crocetin, and safranal may be potential candidate medicines against CVDs. Different in vivo and in vitro studies regarding the beneficial effects of saffron in CVD including arrhythmia, IR, hypertrophy, hypertension, and atherosclerosis were introduced. Saffron was found to attenuate the deleterious effects on the cardiovascular system induced by natural and chemical toxins such as diazinon, doxorubicin, and patulin. Several mechanisms including antioxidant, antiapoptotic, hypolipidemic, antiinflammatory, vasodilator, and improvement of antioxidant defense systems are involved in cardiovascular protection induced by saffron.

This chapter also suggests that after randomized clinical trials saffron may be considered as a preventive or therapeutic agent against CVDs.

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