A Review on the Effects of Saffron Extract and its Constituents on Factors Related to Neurologic, Cardiovascular and Gastrointestinal Diseases

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Abstract

Background: Saffron (*Crocus satious* L.) provides a variety of promising preventive and therapeutic effects with non-considerable side effects.

Objective: Based on our knowledge, this is the first study that simultaneously has reviewed the effect of saffron extract and its constituents on the factors associated with neuropsychological, cardiovascular, and gastrointestinal tract diseases.

Methods: To search studies, an open-ended, language-restricted (English) search of MEDLINE (PubMed) and Science direct databases were conducted (up to 28 October 2014) using specific search criteria to identify all related studies. In addition the SID and Magiran databases were also searched for Persian articles.

Results: Results show that the saffron and its constituents can be beneficial for prevention and treatment of diseases related to memory and eye. However, studies about analgesic, anti-inflammatory and anti-seizure effects of saffron are few, the results are promising. The effects of saffron and its constituents on anxiety and insomnia have been only studied in animal models and the results are promising. Their antidepressants effects are also very evident. On the other hand, the effects of saffron and its active constituents in prevention and treatment of cardiovascular diseases have also been observed in previous studies. Although the studies about saffron effects on gastrointestinal diseases are few and only in animal models, they have shown potential benefits in prevention and treatment.

Conclusion: It seems that saffron and its constituents have preventive and therapeutic roles in neurologic, cardiovascular and gastrointestinal diseases. These functions are contributed to antioxidant, anti-inflammatory and anti-apoptotic properties of saffron.

Keywords: Cardiovascular disease, Crocetin, Crocin, Gastrointestinal disease, Neurologic disease, Safranal, Saffron

Introduction

Diseases of the nervous system

Today diseases of the nervous system are known as a group of diseases with very heavy social and economic burdens. One of the most common types of these diseases are memory related ones including Alzheimer's disease (AD). AD is strongly related to inflammation and oxidative stress [1]. Epilepsy is one of the other diseases of nervous system that affects more than 1% of the population of each society [2]. Unfortunately, not only the medical therapies to prevent epileptic seizures have side effects but also they have no beneficial effects in one third of the patients [3]. Another group of diseases related to the nervous system, are eye diseases. Eye diseases are the major public health problem throughout the world, so that, it is estimated that about 45 million people all around the world are blind. 135 million people suffer from serious eye problems [4, 5]. Developing countries, including Asian countries, have suffered greatly from these diseases [6].

Pain is another annoying factor related to nervous system. Pain defines as an unpleasant sensation and emotional experience associated with actual or potential tissue damages [7]. Pain causes a heavy economic and social burden on societies. The annual cost of pain in the United States is estimated to be about 40 billion dollars [8].

Depression is a major health problem throughout the world, so that, depressive disorders are expected to be the second leading cause of the diseases burdens throughout the world in 2020 [9]. Approximately, 11.3% of adults are diagnosed to suffer from depression annually. Lifetime prevalence of depression in advanced countries is considered to be 21% [10]. Many herbs have psychotropic effects and fewer side effects in comparison of drugs. Their beneficial effects may be greater than the conventional medications. Therefore, using the herbs can be considered as an alternative way to treat depression [9, 10].

Anxiety is the response of brain to danger in order to stimulate the organism to deal with it [11]. Anxiety disorders are the most common class of mental disorders [12]. The average prevalence of these disorders during the lifetime is estimated to be 25% [12, 13]. Although pharmacological and psychological interventions are the leading approaches to treat anxiety, herbs may provide another safe and effective option for the treatment [14].

Cardiovascular disease

Cardiovascular diseases are the most important causes of death not only in the world, but also in Iran. Approximately, 30% of the mortality in the world and about 38% in Iran are due to these diseases. According to experts, three thousand years of useful life in Iran is lost daily due to the cardiovascular diseases [15-17].

Among cardiovascular diseases risk factors, hypertension and atherosclerosis are the most common ones [18, 19]. Hypertension is a chronic disease, and its prevalence in the world and in Iran has increased in recent years, and is still increasing. Hypertension leads to several complications, including stroke, heart attack, and renal and eye diseases. Another important cardiovascular disease is type 2 diabetes. Type 2 diabetes is a chronic disease with an increasing prevalence in the world. The prevalence of diabetes in the world has increased five times over the past 50 years. Consequently, 285 million people suffer from diabetes all over the world [20].

Gastrointestinal diseases

Majority of the general and internal clinics patients are the ones who complain about

gastrointestinal symptoms. Genetic, psychological, lifestyle and diet factors play an important role in development of the diseases [21]. The diseases have large socioeconomic impacts on community. Hence, 11 % of the American population suffers from gastrointestinal diseases and their prevalence in the population over the last 65 years is 35% [22, 23].

Saffron

Saffron (*Crocus satious* L.) is an expensive traditional spice. Dried stigma of saffron has been used as a spice for many years [24, 25]. The world's annual production of saffron is estimated to be 300 tons (76% of the total production in Iran). Documents prove that this native Iranian plant was used as a food spice in the Achaemenid ages [26, 27].

Beside its traditional usage as a spice, saffron has known as a stomach pain soother, antispasmodic, digestion aid, renal colic pains reliever, antidepressant, and appetizer agent in Iranian traditional medicine [28, 29]. The stigma is the most used part of the saffron in cooking. The saffron (dried stigmas) beneficial effects are due to three main secondary metabolites including soluble crocin (mono-glycosyl or di-glycosyl polyen esters) and its derivatives which are responsible for its special color, picrocrocin (mono-terpene glycoside precursor of safranal and product of Zeaxanthin degradation), which is responsible for its bitter taste, and safranal which is responsible for its especial odor. Picrocrocin constitutes of 1 to 13 % of dry saffron weight. Safranal (fat soluble) and pigments of the crocetin carotenoid (a natural di-carboxylic acid carotenoid precursor crocin) are bitter, but the most important cause of saffron bitterness is picrocrocin. Color compounds of saffron are including crocetin carotenoids and glycosidic forms of di-gentiobioside (crocin), gentiobioside, glycoside, gentio-glycoside and Beta-crocetin di-glycoside (mono-methyl ester), gama-crocetin (di-methyl ester), alpha-carotene, beta-carotene, lycopene and Zeaxanthin. Saffron lipophilic carotenoids are lycopene, alpha-and beta-carotene and zeaxanthin. Kampferol has also found in alcoholic extract of saffron petals. Flavonoids especially lycopene, amino acids, proteins, starch, resins and other compounds have also been found in saffron. Saffron also has trace amounts of thiamine and riboflavin [30-39]. Different therapeutic effects of saffron have been shown in previous studies, and majority of these beneficial effects are contributed to antioxidant and anti-inflammatory properties of saffron extract and constituents [40, 41]. This study is the first review on saffron extract and its constituent's effect on the factors associated with the nervous system, cardiovascular and gastrointestinal diseases.

Materials and Methods

This is a review article. In order to search the related studies, an open-ended, language-restricted (English) search of MEDLINE (PubMed) and Science direct databases were conducted (up to 28 October 2014), using specific search criteria to identify all related studies, with the keywords that provided from MESH. The keywords used were included saffron, crocin, crocetin, safranal, colchicum, nervous system disease, Alzheimer disease, memory, learning, eye disease, anticonvulsant, anxiety, depression, anxiolytic, premenstrual syndrome, insomnia, cardiovascular disease and gastrointestinal disease. For finding the Persian articles, SID and Magiran databases were searched. Interventional studies in human populations, In vitro and In vivo animal

studies were considered. Articles in which the active components of saffron were obtained from a source other than saffron and articles in which the used saffron were belonged to a very special race other than conventional saffron were excluded from the review process.

Results

The effects of Saffron on nervous system diseases

1- Effect on learning and memory

Neurodegenerative diseases of the central nervous system are often associated with impairment of memory and other cognitive functions [24]. Akhondzadeh and colleagues treats 54 patients with mild-to-moderate AD randomly with 30 mg of saffron extract, or 10 mg /kg donepezil per day in a multicenter clinical trial. After 22 weeks, saffron extract could improve mild-to-moderate AD as same as donepezil [42]. A similar study by Akhondzadeh et al, studied the effect of saffron extract on 46 patients with mild-to-moderate AD during 16 weeks. Patients randomly received 30 mg/day saffron or placebo capsules. The patients in saffron group had a better cognitive performance compared to placebo group ($p = 0.04$) [43]. Khalili and et al studied effect of crocin (15 and 30 mg/kg) on AD induced by streptozocin (STZ) in male Wistar rats. The results showed the beneficial effect of 30 mg/kg crocin on antagonize cognitive disorders induced by STZ, and it's potential to treat diseases such as AD [44]. In another study designed by the same group, the results have shown that the saffron extract (60 mg/kg) inhibit the memory impairment in AD induced by STZ in the rats [45]. Oral intake of 125 to 500 mg/kg of saffron extract alone had no effect on learning in mice [46], and 50 to 200 mg/kg crocin alone was also ineffective [47]. However, high doses of crocin alone in the intraventricular injection (150 nM) improved the hippocampus function [24]. Hosseinzadeh and et al in 2012 have injected aqueous solution of crocin and hydroalcohol extract of saffron in different doses in a rat model of chronic cerebral hyperfusion. They found that saffron extract and crocin improve spatial cognitive abilities following chronic cerebral hypoperfusion in male Wistar rats. It is assumed that antioxidant properties of saffron and crocin may be probable mechanism of action [48].

Several Japanese studies have reported that saffron extract and its two major constituents (crocin and crocetin), improve the learning skills and memory in mice and rats with impaired learning and memory caused by ethanol [24, 46, 49-52]. Oral intake of Saffron at doses 125-250 mg/kg or intraventricular injection of crocin (2.51 nM) significantly inhibit ethanol-induced hippocampus damages in rat [51, 52]. However, intraventricular injection of picrocrocin (2.51 nM) in a similar study by Abe and colleagues had no such effect [24]. Sugiura and et al have shown that crocetin gentiobiose glucose ester (with a glucose less than crocin) inhibits (but with a lesser extent than crocin) ethanol effects on hippocampus [50]. Hosseinzadeh and Ziaei study in 2006 have investigated the effects of saffron extract, crocin and safranal on intact memory and hyoscine induced learning deficits on rat. However, saffron extract and its crocin and safranal have not any effects on intact memory, saffron extract and crocin, but not safranal, in doses of 0.0025 gr/kg and 200 mg/kg respectively, have inhibited the hyoscine impaired acquisition/performance activity [53].

About assumed mechanisms, Abe and et al study has found that crocin antagonize N-methyl-D-aspartate receptor dependent response inhibition in the neurons of hippocampus [54]. These beneficial effects of saffron can be contributed to the antioxidant and anti-amiloidogenic (preventing the aggregation and deposition of beta amyloid in brain) functions, boosting cholinergic action, and protecting neurons by saffron [28, 44, 55].

In conclusion, according to the studies it seems that the saffron and its constituents (especially crocin) improve the memory function in patients suffering from memory disorders and antagonize the external degeneration of the memory.

2- Effect on ocular blood flow and retinal function

Marangoni and et al studied the effect of oral intake of saffron (20 mg/day) for 11 months on 33 patients with primary age-related macular degeneration (AMD) who had the risk genotypes. Saffron improved the sensitivity of the retina and its function, but there was no difference between genotypes, which means that the effect of saffron had no relation with the major risk genotypes of the disease, and this effect is related to the reduction of oxidative stress [56]. Falsini and et al have compared the effect of saffron (20 mg/day orally) with placebo in 25 patients with primary AMD. After three months supplementation, the two groups were exchanged and the study continued for three more months. This Study proved that short-term intake of saffron improves retinal flicker sensitivity in AMD [57]. In another study Piccardi and et al have studied the effect of long term intake (14 months) of saffron (20 mg per day) on 29 patients with primary AMD. The study has also shown the effect of saffron on improving the macular function and visual quality. The authors attributed this effect to crocin and crocetin [58]. It is said that crocin inhibits the apoptosis and thus light induced death of the separated photoreceptors, While crocetin increases oxygen diffusion into the fluids (eg, plasma) [59]. Xuan and et al have found that crocin analogs isolated from saffron significantly increase the blood flow to the retina and choroid and improve the retinal function. The authors have concluded that the crocin analogs can be used to treat AMD and ischemic retinopathy [60]. In another study on rats by Maccarone and et al, saffron, through 24 hours of light exposure, has inhibited the photoreceptor damage and upregulation of fibroblast growth factor [61]. It has been found in an in vitro study that saffron may protect the photoreceptors from oxidative stress. This action has contributed to the anti-inflammatory and antioxidant properties, and possibly to apoptosis regulation by saffron [62]. Recently, Jabbarpoor Bonyadi and et al, have studied the effect of saffron on ocular blood pressure in patients with glaucoma. The results show hypotensive effect of saffron after one month treatment with saffron aqueous extract compared with placebo [63].

In Conclusion, it seems that saffron and its constituents (especially crocin and crocetin) can play role as an eye protection. These effects can be contributed to the antioxidant and anti-inflammatory properties, and inhibition of apoptosis by saffron and its constituents.

3- Anticonvulsant effect

Khosravan in 2002 has found that after inducing artificial seizure by maximum electroshock (MES) and pentylene tetrazol (PTZ), aqueous and alcoholic extracts of saffron (at doses of 0.8 and 2 g/kg,

respectively) have shown anticonvulsant effects. This study has shown that the saffron extract may be useful in the treatment of absence and tonic-clonic seizures [64]. Hosseinzadeh and Sadeghnia have studied the effect of intracerebroventricular injection and peripheral administration of safranal in different doses on pentylenetetrazol induced seizures in rats. Safranal in peripheral administration but not in intracerebroventricular injection decreased the incidence of both minimal colonic (145.5 mg/kg body weight) and generalized tonic–colonic (145.5 mg/kg body weight) seizures. The authors have resulted that probable mechanism of action may be modulation of $GABA_A$-benzodiazepine receptor complex by safranal [65].

Sadeghnia and et al in 2008 have investigated the effect of a single intraperitoneal administration of safranal (291mg/kg) on acute experimental seizure models. The results have indicated that safranal may have some antiabsence seizure properties by modulating Gama Amino Butyric Acid (GABA) receptor activity [66].

4- Anti-nociceptive effects

An in vivo study by Hosseinzadeh and Younesi on mice has shown that the extract of saffron stigma and its petal, in different doses, have analgesic and anti-inflammatory (acute and chronic) effects. The results indicate that aqueous and alcoholic extracts of saffron stigma at doses less than 0.8 and 2 g/kg (LD_{50}) respectively, and the aqueous and alcoholic extract of saffron petal at doses 3.6 and 8 g/kg (LD_{50}) respectively, exert their beneficial effects [67]. These effects may be due to the flavonoids, tannins, anthocyanins, alkaloids and saponins of saffron [68]. Amin and Hosseinzadeh have shown that intraperitoneal administration of ethanolic and aqueous extracts of saffron in different doses (50, 100 and 200 mg/kg) and its constituent, safranal (0.025, 0.05 and 0.1 mg/kg), can dose dependently attenuate behavioral symptoms of constriction injury induced neuropathic pain in rats. However, crocin even at a high dose of 50 mg/kg did not have any protective effect [69]. Subsequent study of Amin and et al demonstrated that protective effects of ethanolic and aqueous extracts of saffron at an effective dose of 200 mg/kg intraperitoneal may be due to attenuation of proinflammatory cytokines, oxidative stress and apoptosis [70]. An animal study by Hosseinzadeh and Shariaty in 2007 on mice demonstrated antinociceptive effects of intrapritoneal administration of safranal in writhing (0.1, 0.3 and 0.5 ml/kg), hot plate (0.5 ml/kg) and formalin (0.05 ml/kg) tests [71].

In conclusion, it seems that saffron may indicate analgesic effects on animal models of pain. According to mentioned studies, this beneficial effect may be attributed to safranal. Howevere, clinical studies are needed to affirm the results.

5- Effect on anxiety and insomnia

Pitsikas and colleagues in 2008 compared anxiolytic effects of crocin and diazepam in rats. Intraperitoneal injection of crocin at the highest dose (50 mg/kg) reduced the anxiety in rats as same as diazepam. However, lower doses (15 to 30 mg/kg) had no such effects. The mechanism of this effect is unknown [72]. Hosseinzadeh and Nouraei compared sleep status and anxiety of rats treated with saffron, safranal or crocin. Saffron at doses of 56 and 80mg/kg caused a significant reduction in anxiety and at a dose of 560 mg/kg significantly improved sleep in mice. Safranal had anxiolytic effect at doses of 0.15 and

0.35 mg/kg, whereas crocin had no significant anxiolytic effect. The results have shown differences in the effects of saffron and its constituents, so, the beneficial effects of saffron constituents can increase synergistically in the saffron [73].

In conclusion, it seems that saffron has anxiolytic and anti-insomnia effects in animal models. These effects are dose dependent and more considerable from saffron than its constituents. Further studies are needed to identify the mechanisms of saffron effects.

6- Effect on depression

For the first time, Akhondzadeh and et al, studied the effect of alcoholic extract of saffron in the treatment of mild-to-moderate depression [9, 10, 74]. In the 2004 study, they compared the effect of saffron at a dose of 30 mg/day with antidepressant imipramine (100 mg/day) in 40 patients with mild-to-moderate depression during 6-weeks. There was no significant difference between the two groups in improvement of the symptoms [74]. In the 2005 study, they found that saffron (30 mg/day) compared with placebo significantly improve the mild-to-moderate depression during 6-weeks [10]. In another study by Marangoni and et al on 40 patients with mild-to-moderate depression (35 patients have completed the study), 6 weeks of supplementation with saffron (30 mg/day) improved symptoms of the disease more than the placebo [56]. Akhondzadeh and colleagues found that saffron at a dose of 30 milligrams per day in 40 outpatients with depression after 8 weeks, was more effective in comparison with antidepressant fluoxetine (10 mg/day) [9]. In Noorbala and colleagues study on 40 patients with mild-to-moderate depression, saffron at a dose of 30 mg/day for 6 weeks was effective in reducing the symptoms as same as fluoxetine (20 mg/day) [75]. These two studies have suggested the inhabitation of dopamine, norepinephrine and serotonin reuptake by crocin and safranal as possible mechanisms for anti-depressive effects of saffron [9, 75]. In Moshiri and et al study, alcoholic extract of saffron petals at a dose of 30 mg/day has reduced symptoms of depression compared with placebo after 8 weeks [76]. Aghahosseini and et al have found that saffron, after 8 weeks, reduces symptoms of depression in women with premenstrual syndrome compared with placebo group [77]. In Melnyk and et al study, kaempferol (the active constituent in saffron petals) at doses of 100 and 200 mg/kg in mice and 50 mg/kg in rat reduces depressive symptoms as same as fluoxetine [41]. Hosseinzadeh and colleagues have compared saffron (crocin, safranal, aqueous and alcoholic extract of saffron), fluoxetine and imipramine effects on reducing symptoms of depression in mice. Crocin in different doses and safranal at a dose of 0.5 mg/kg have improved symptoms of depression. Alcoholic extract at doses of 200 and 800 mg/kg and aqueous extract at doses of 160 and 320 mg/kg have reduced sedentary time compared with normal saline and have improved mice action compared with fluoxetine. The authors have found that crocin probably affects the dopaminergic system and inhibits reuptake of norepinephrine and safranal probably affects the serotonergic system [78]. The authors have also reported that saffron increases serotonin levels in brain. The mechanism is unclear but saffron may inhibit the reuptake of serotonin in synapses [79, 80]. Based on the animal models, Berger and colleagues have concluded that the inhibition of monoamine and agonizing N- Metyl- D- aspartate reuptake and improvement of brain-derived neurotrophic factor signaling can be the other effective

mechanisms [81]. Hassani et al have studied the effects of crocin on behavioral functions, and transcription and protein levels of cAMP response element binding protein (CREB), brain-derived neurotrophic factor (BDNF), and VGF (non-acronymic) in hippocampus of rats. Crocin in doses 25 and 50 mg/kg increased the levels of CREB and BDNF, and increased the VGF levels (12.5, 25, and 50 mg/kg). Transcription only significantly increased by 12.5 mg/kg crocin for BDNF. These changes are similar to changes induce by antidepressant drugs [82]. A similar recent study by Ghasemi et al has demonstrated that saffron aqueous extract in doses 40, 60 and 80 mg/kg/day significantly increase BDNF and CREB protein levels and transcript levels of BDNF [83].

In conclusion, likely saffron and its constituents are as effective as the most commonly used antidepressants in treating mild-to-moderate depression. These effects may contribute to the anti-inflammatory and antioxidant properties of saffron.

7- Effect on premenstrual syndrome (PMS)

Aghahosseini and colleagues have investigated the effect of saffron petals on women with PMS symptoms. The patients consumed 30 mg/kg saffron or placebo. The results have shown a significant improvement of symptoms in saffron group compared to before treatment and in saffron group compared to controls [77]. However, further studies are needed to confirm this effect and to find possible mechanisms.

Saffron effects on the cardiovascular system diseases

1- Effect on coronary heart disease and insulin resistance

Some studies have found the effect of saffron constituents in the treatment of atherosclerosis [84-86]. In an Indian study (1998) by Verma and et al, patients with coronary heart disease (CHD) consumed 50 mg of dissolved saffron (dissolved in 100 ml of milk) twice a day. There was a significant reduction in lipoprotein oxidation susceptibility which has contributed to antioxidant properties of saffron [87]. In 2005, Zheng and et al compared the effect of crocetin with placebo in rabbits treated with high lipid diet (HLD) for 8 weeks. Hypercholesterolemia and atherosclerosis was reduced in crocetin group. Although there were no significant changes in plasma lipids in both groups, It has suggested that the crocetin inhibits the activation of nuclear factor NF-kB in the aorta, and consequently inhibits the expression of cell adhesion molecule 1 (VCAM-1) [86]. In 2007 a similar study was conducted by He and et al in quail. Crocin and crocetin (25, 50, and 100 mg/kg/day, respectively) significantly inhibited the increase of total cholesterol, LDL, VLDL, malondialdehyde (MDA) and increased aortic intima thickness, accumulation of foam cells and serum nitric oxide (NO) levels [85]. Sheng and et al in 2006 have found that crocin at a dose of 100 mg/kg/day in rats, reduces the increased TG, total cholesterol, LDL and VLDL levels compared to controls. The study has also shown that crocin inhibits gastric and pancreatic lipase, although, the mechanism is unknown [88]. Mehdizadeh and et al have studied the effects of saffron extract and crocin on myocardial infarction induced by isoproterenol in Wistar rats. Saffron extract and safranal caused levels of LDH, CK-MB, myocardial lipid peroxidation and malondialdehyde (MDA) increased less and myocardial injury occurred less than controls. This effect seems to take place through the regulation of oxidative stress [89]. Other

studies have shown that saffron and its constituents reduce lipid peroxidation in kidney, hippocampus and skeletal muscle during reperfusion oxidative damage in rats [90 - 92].

Xi and colleagues in 2005, have treated rats with dexamethasone or dexamethasone + crocetin for 6 weeks in order to induce insulin resistance. In the second group, the serum levels of insulin, free fatty acid, TG and TNF-α were significantly lower. However, the mechanism is unknown [93]. Xi and colleagues in a similar study in 2007, have studied the effect of crocetin on high-fructose diet treated rats. Blood pressure, epididymal adipose tissue, TG, free fatty acids, LDL, HDL and serum insulin levels were lower in the crocetin group [94]. Other studies have shown that crocetin (or crocin) can alleviate atherosclerosis and related diseases such as hypercholesterolemia, hypertension, insulin resistance, hyperlipidemia, hypertriglyceridemia and hyperinsulinemia [84, 86-88, 93, 94]. However, most of these studies have used crocetin from sources other than saffron [84, 85, 88, 93]. In conclusion, it seems that saffron and its constituents (especially crocin and crocetin) protect the cardiovascular system; this can be contributed to their antioxidant properties. The evidence have also shown the effect of saffron and its constituents on insulin resistance, but it needs further studies to confirm these effects and to find the mechanisms.

2- Effect on blood pressure

Fatehi and et al studied the effect of saffron petal extract on blood pressure in anesthetized rats and in stimulated isolated rats vaz deferen and ileum of guinea pig. Blood pressure was reduced with a dose-response procedure in presence of the extract in the rats. The dose of 50 mg/100 g of aqueous extract was the minimum dose that has beneficial effect. There was a significant reduction in stimulated blood pressure in the rats' vaz deferen and guinea pig ileum in a dose of 560 mg/mL of the aqueous extract [95]. Razavi et al have investigated the effect of crocin on systolic blood pressure of diazinon administrated rats. The study showed that crocin at doses of 12.5, 25 and 50mg/kg attenuate hypotensive effect of diazinon. The authors have assumed antioxidant properties of crocin as effective mechanism of action [96]. In 2010, Imenshahidi et al have administrated hypotensive and desoxycorticosterone acetate-induced hypertensive rats by saffron aqueous extract (2.5, 5 and 10mg/kg), crocin (50, 100 and 200mg/kg) and safranal (0.25, 0.5 and 1mg/kg), intravenously. The aqueous extract of saffron, crocin and safranal have dose-dependently reduced the mean arterial blood pressure in normotensive and hypertensive rats. The authors have resulted that safranal may be the main constituent of saffron for lowering blood pressure [97]. Recently, Imenshahidi et al have conducted a similar study. They administrated hypotensive and desoxycorticosterone acetate-induced hypertensive rats with crocin (50, 100 and 200mg/dl) for 5 weeks. Crocin reduced mean arterial blood pressure in hypertensive rats, but not in hypotensive animals, with a dose dependent manner [98].

In conclusion, saffron extract and its constituents, especially crocin and safranal, have some blood pressure modulating properties. However, its need additional investigations to find effective dose and mechanism of action, the effect may be contributed to antioxidant properties of saffron and its constituents.

Saffron effects on gastrointestinal diseases

1- Effect on gastric and digestive disorders

Plants and I. Karaj in 2009, studied the effects of saffron alcoholic extract (at doses of 25, 100 and 250 mg/kg), crocin (at doses of 2.5,5 and 10 mg/kg) and safranal (at doses of 0.25, 2 and 5 ml/kg) on rats with gastric ulcers. They were all useful in ulcer recovery as same as omeprazole. The study has found that these compounds have antioxidant properties and inhibit gastric ulcer formation by a dose dependent inhibition of mucosal damage induced by indomethacin. The authors have considered the increased levels of glutathione and inhibition of lipid oxidation as the mechanisms (99). Xu and et al have studied the effect of crocin in different doses on gastric ulcers in indomethacin treated rats. The results have shown that damages are inhibited in crocin group compared with controls. Crocin, even at high doses (50mg/kg), have not caused gastric ulcer (100). Inoue and et al have studied the effects of N-095 (a drug containing 90 mg of saffron in daily dose) and histamine on stress-induced gastric ulcer in rats. The N-095 has inhibited gastric ulcers induced by histamine or stress. However, the drug has other active components that the beneficial effects can be contributed to them (101). In Nabavizadeh and et al study, there was a beneficial effect from saffron on digestion. In this study, increased gastric acid and pepsin secretion in rats consumed saffron (100mg/kg) has been observed. The researchers have assumed that saffron may activate nitric oxide synthase (NOs), then release histamine and result in gastric acid and pepsin secretion [102]. It seems that saffron and some of its active constituents (crocin and safranal) may be protective in gastric ulcers and facilitate food digestion. The possible mechanisms can be contributed to the antioxidant properties of these compounds. However, further studies are needed to confirm these effects and to identify the accurate mechanisms.

Discussion

The results show that saffron and its constituents can protect the nervous system neurons against internal and external damages; so inhibit memory degeneration of patients with Alzheimer disease and even may be effective in their treatment. This neuroprotective effect is also considerable for the eye, so that saffron and its constituents have reduced eye problems in diseases such as Age-Related Macular Degeneration (ARMD). Although there are few studies about analgesic, anti-inflammatory and anti-seizure effects of saffron, the results have been promising and focus on the importance of further human and animal studies in this area. The effect of saffron and its constituents on anxiety and insomnia have studied only in animal studies; therefore human studies are particularly important in this area. The effects of saffron against anxiety and insomnia are dose dependent and more visible from saffron than its constituents. So, it seems that saffron constituents act synergically. The effect of saffron on depression is so visible in human and animal studies that can be considered as effective as commonly used drugs. However, the studies are short-term; and long-term effects and safety of saffron are unclear. There are some limitations in the studies design, such as they are single-center, all have been done in Iran, have used saffron in same doses, their sample size is small, all have used a similar scale to assess depression, they have not had any follow-up period, and their information about participants was limited.

On the other hand, the effects of saffron and its active constituents in prevention and treatment of cardiovascular disease have been found in previous studies. The lipid-lowering effects were so strong that reducing the fatty deposits in artery walls has also been seen. About insulin resistance, despite of the studies that have shown the beneficial effects of saffron and its constituents, more researches are needed to confirm these effects and the possible mechanisms. Animal studies have investigated the effect of saffron petals in hypertension, but due to the antioxidant and anti-inflammatory properties of saffron and its active constituents, it seems that they may be potentially effective in reducing blood pressure, so, we recommend other researchers to study this effect for future researches. There are few studies about saffron effects on gastrointestinal diseases; and there is no human study. Due to the beneficial results of animal studies about saffron effect on peptic ulcer and food digestion, the need for human studies to confirm these results, and animal and human studies to detect other gastrointestinal effects of saffron and its constituents is considerable.

Conclusion

In conclusion, it seems that saffron and its active constituents (crocin, crocetin and safranal) play a protective and therapeutic role in the nervous system, cardiovascular and gastrointestinal diseases (Table 1). These functions have contributed to antioxidant, anti-inflammatory and anti-apoptotic effects of them. As there are few long-term human studies and few studies have used saffron (other than its constituents) in this area, further researches are recommended.

Table 1- Some studies about therapeutic roles of saffron and its active constituents in the nervous system, cardiovascular and gastrointestinal diseases

Effect	Saffron or its constituents	Study type	observations	sources
Anti-Alzheimer disease	Saffron extract	Multicenter randomized controlled clinical trial	Saffron can alleviate mild-to-moderate depression as same as Donepezil	[43]
Anti-Alzheimer disease	Saffron extract	randomized controlled clinical trial	Saffron cause better cognitive function than placebo	[42]
Anti-memory problems effect	Crocin	Male Wistar rats	Crocin reduce cognitive disorders induced by STZ	[44], [45]
Effect on retinal sensitivity and function in patients with Age-related macular degeneration	Saffron extract	randomized controlled clinical trial	Saffron improved retinal sensitivity and function	[56]

Table 1- Continued

Effect	Saffron or its constituents	Study type	observations	sources
Effect on Age-related macular degeneration	Saffron extract	Cross-over randomized double-blind controlled clinical trial	Saffron short-term supplementation alleviate flicker sensitivity of retinal	[57]
Anticonvulsant effect	Saffron extract	In mice	Saffron demonstrate anticonvulsant effect	[64]
Anti-inflammatory and analgesic effect	Petal and stigma extract of saffron	In mice	Petal and stigma extract of saffron have analgesic and anti-inflammatory (acute and chronic) effects	[67]
Anti-anxiolytic effect	Crocin	In rat	Intraperitoneal injection of crocin in the highest dose (50 mg/kg) has reduced anxiety symptoms as same as Diazepam	[72]
Effect on sleeping function, anxiety and momement	Saffron extract, safranal and crocin	In mice	Saffron extract has anxiolytic effect, and improve sleeping function and movement balance. Safranal has only anxiolytic effect, while crocin has not any significant effect	[73]
Anti-depression effect	Saffron extract	randomized placebo-controlled clinical trial	Saffron alleviated mild-to-moderate depression compared with placebo	[10]
Anti-depression effect	Saffron extract	randomized double-blind clinical trial	Saffron extract has reduced depression symptoms as same as Fluoxetine	[9]
Effect on premenstrual syndrome	Saffron petal extract	randomized double-blind controlled clinical trial	Saffron alleviated premenstrual syndrome symptoms intra saffron treated group and compared with placebo treated group	[77]
Effect on lipoproteins oxidation	Solute saffron	randomized double-blind clinical trial	Saffron reduce lipoproteins sensitivity to oxidation	[87]

Table 1- Continued

Effect	Saffron or its constituents	Study type	observations	sources
Effect on hypercholesterolemia and atherosclerosis	Crocin and crocetin	In quail	Crocin and crocetin reduces hyperlipidemia and alleviates athrosclerosis	[85]
Effect on myocardial infarction	Saffron extract and safranal	In Wistar rat	injection of saffron extract or safranal in different doses alleviates myocardial damages	[89]
Effect on insulin and lipids levels in the serum	crocetin	In rat	Crocetin reduce insulin and lipids levels in the serum	[94]
Effect on blood pressure	Petal extract of saffron	In vivo (In rat) – In vitro	Saffron petal extract reduce blood pressure in the rats and in stimulated Vaz deferens	[95]
Effect on gastric ulcer	Saffron extract, crocin and safranal	In mice	Saffron extract, crocin and safranal alleviates gastric ulcers as same as Omeprazole	[99]
Effect on digestion	Saffron extract	In mice	Saffron improve digestion by increase in gastric acid and pepsin	[102]

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