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Therapeutic effects of crocin: A review of recent studies

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ABSTRACT

Crocin is a plant ingredient mainly found in the extract of *Crocus sativus* (Saffron). This carotenoid compound has antioxidant, anti-inflammatory, antitumor, and antihypertensive properties. This review summarizes the therapeutic effects of crocin. Data were retrieved from 2015 until the end of April 2025 using databases including the Web of Science, PubMed, Scopus, and Google Scholar. According to the findings of previous studies, the therapeutic effects of crocin on various organs can be attributed to its ability to scavenge free radicals, enhance antioxidant activities, reduce inflammatory reactions, and modulate the PI3K/AKT, NF-κB, and PPARγ/LXRs signaling pathways.

KEYWORDS: Crocin; Oxidative stress; Inflammation; Antioxidant; *Crocus sativus*

1. Introduction

The effects of natural compounds are increasingly being investigated to alleviate and treat ailments. Crocin is a water-soluble carotenoid derived from *Crocus sativus* (Saffron)[1]. This herbal plant possesses various biological activities such as antioxidant, anti-inflammatory, and antihypertensive activities[2,3]. In women with polycystic ovary syndrome (PCOS), crocin could alleviate inflammation by reducing the level of inflammatory markers[4]. In aged male rats, crocin diminished the harmful impacts of ethanol and nicotine on learning and memory processes[5]. Moreover, in a rat model of streptozotocin-caused type 2 diabetes, crocin modified the increased level of glucose and oxidant biomarkers, thus ameliorating diabetes[6]. A previous study showed that crocin prevents bone loss by inhibiting oxidative stress and suppressing ferroptosis *via* the Nrf2/GPX4 signaling pathway[7]. As demonstrated in *in vivo* and *in vitro* studies, crocin also suppresses uncontrolled cell proliferation and exerts positive therapeutic effects against cancer cells[8,9]. Considering a broad spectrum of therapeutic benefits of crocin, this review article aimed to summarize its advantageous effects on body systems.

2. Method

In this article, the data of the studies on crocin were obtained *via* databases including the Web of Science, PubMed, Scopus, and Google Scholar using keywords "crocin" and "nervous system", "cardiovascular system", "respiratory system", "gastrointestinal tract", and "urinary system". Relevant published studies were selected from 2015 to the end of April 2025.

Summary

Question: Can crocin be considered an effective therapeutic strategy for preventing organ damage?

Findings: Recent studies showed that crocin protected different body systems mainly *via* modulating oxidative stress and attenuating inflammatory pathways. However, its therapeutic effects have not been fully understood in human studies.

Meaning: Crocin has been recommended as an herbal active compound for improving disorders of the body systems; however, further assessments are required to verify its application and safety in humans.

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3. Effect of crocin on the nervous system

Stressful stimulants can disturb the normal function of the nervous system and induce anxiety- and depression-like behaviors[10]. Stressful conditions can also exert harmful effects on learning and memory processes and synaptic plasticity[11]. The effect of 30 mg/kg of crocin alone and in combination with alcoholic extract of *Terminalia chebula* against chronic restraint stress-caused brain disturbances was evaluated in an animal model. The behavioral results demonstrated that use of crocin and *Terminalia chebula* extract for 14 consecutive days prevented anxiety-like behaviors and memory deficits in rats exposed to stress. Based on electrophysiological studies, crocin also ameliorated synaptic plasticity in CA1 area of the hippocampus[12]. The findings of elevated plus maze, passive avoidance test, and Barnes maze test exhibited that treatment with nano-chitosan containing 160 mg/kg of crocin for 14 consecutive days had positive effects on learning and memory indices and anxiety in rats with chronic immobilization stress[13].

Neuroinflammation upsets cell homeostasis and can occur by overactivation of neuroglia, such as astrocytes and microglia in the nervous system[14]. Infections[15] and neurological diseases, including Alzheimer's disease, Parkinson's disease, and multiple sclerosis (MS), have a principal role in brain inflammation[16]. Su *et al.* demonstrated that the administration of 40 mg/kg of crocin for 14 days improved spatial memory *via* modulating the PI3K/AKT signaling pathway and decreasing the levels of inflammatory cytokines, including TNF-α, IL-1β, and IL-6[17].

MS is a chronic inflammatory disease of the central nervous system resulting from destruction of myelin sheath of the nerve cells[18]. This autoimmune disease is characterized by sensory and motor disorders. The studies show that MS may induce cognitive disturbances[19]. In an animal study, crocin exerted the memory-enhancing effects against ethidium bromide-induced MS by improvement of sensory and motor behaviors and increased levels of brain-derived neurotrophic factor, and nerve growth factor 1 in the brain of the rats[20]. Another study investigated the effects of crocin on cuprizone-caused MS. The results of behavioral tests revealed that crocin reduced motor disorders caused by cuprizone. In addition, crocin decreased the serum level of malondialdehyde (MDA) and increased the blood concentration of glutathione peroxidase (GPx) and superoxide dismutase (SOD)[21]. In a human study, patients with MS received tablets containing 15 mg crocin twice a day for 8 weeks. The treatment significantly lowered the serum level of C-reactive protein, MDA and NO[22]. In patients with Parkinson's disease, use of 30 mg crocin capsules for 8 weeks ameliorated movement activities and neuronal oxidative injuries[23].

Lipopolysaccharide (LPS) is a biological molecule evoking the immune responses. This bacterial toxin can also impair learning and memory processes by inducing brain oxidative stress and neuroinflammation[24]. In male Wistar rats exposed to 1 mg/kg of LPS, 100 mg/kg of crocin successfully prevented destructive impacts of LPS on spatial learning and memory by inhibiting lipid peroxidation, downregulating the expression of caspase 3, TNF-α, and NF-κB in the brain[25]. Trimethyltin chloride is a toxic compound that causes brain damage. It has been demonstrated that peripheral injection of trimethyltin chloride induces cognitive deficits[26]. Administration of 10 and 50 mg/kg of crocin for 3 weeks could alleviate trimethyltin chloride-caused cognitive deficits in rats by increasing the activity of SOD and reducing the level of caspase 3 in hippocampal tissue[27].

4. Effect of crocin on the cardiovascular system

Chronic heart failure (congestive heart failure) (CHF) is known as a heart disease in which the heart loses its ability to pump sufficient blood throughout the vascular system[28]. Risk factors such as hypertension, diabetes, and obesity have been listed as the most important causes for CHF[29]. In addition to the use of drugs such as vasodilators and diuretics, employment of effective herbal substances has been recommended as a beneficial therapeutic strategy in reduction of symptoms of CHF[30]. In order to elucidate the mechanism of the effect of crocin on CHF, male Sprague Dawley rats received 0.05, 0.075, and 0.1 mg/kg of this compound for 4 consecutive weeks. It was concluded that a high dose of crocin (0.1 mg/kg) increased calcium concentration in cardiomyocytes and modulated the activity of Na^+-Ca^{2+} exchanger and the type 2a sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA2a)[31].

Cardiac arrhythmia is a type of heart dysfunction resulting from abnormal heart rhythm disturbance. Some cardiac arrhythmias, such as ventricular fibrillation and ventricular tachycardia, can be a result of myocardial infarction (MI)[32]. In addition, it has been suggested that a change in connexin 43 (Cx43) expression is involved in the anti-arrhythmic effects of drugs[33]. Li *et al.* showed that crocin alleviated MI-induced cardiac arrhythmia in rats by upregulating Cx43 expression[34]. Kelch repeat and BTB domain-containing protein 7 (KBTBD7), as a member of BTB-kelch protein family, can activate NF-κB signaling pathway and finally stimulate the production of inflammatory cytokines[35,36]. Therefore, researchers consider it a target to evaluate the effect of anti-inflammatory compounds. The results of Yuan *et al.* demonstrated that crocin at 100 and 200 mg/kg prevented MI-induced cardiac malfunction in rats by reducing inflammatory reactions. This cardioprotective impact of crocin was attributed to the suppression of KBTBD7 expression[37]. Atherosclerosis is an inflammatory disease that takes place when fat and cholesterol accumulate in the walls of arteries[38]. Treatment of this metabolic-related disorder reduces the risk of heart attacks[39]. Additionally, changes in the activity of peroxisome proliferator-activated receptor γ (PPARγ)/liver X receptors (LXRs)/ATP binding cassette transporter A1 (ABCA1) signaling pathway are involved in the pathogenesis of atherosclerosis[40]. In high-fat diet-exposed mice, treatment with 4 mg/kg/day and 12 mg/kg/day of crocin for 12 weeks resulted in the alleviation of atherosclerosis by stimulating the reverse cholesterol transporter and regulating the PPARγ/LXRs pathway[41].

Doxorubicin is an anticancer drug that has been frequently used to suppress cell proliferation in breast cancer and leukemia[42]. Cardiotoxicity is one of the main side effects of doxorubicin[43]. In rats with doxorubicin-induced cardiotoxicity, administration of 40 mg/kg of crocin for 15 days protected heart tissue by lowering MDA, TNF-α, and caspase 3 levels, elevating SOD, CAT, and GSH levels, and modifying lipid profile[44]. Methamphetamine is a chemical substance with strong addiction effects. Besides affecting the central nervous system, methamphetamine has been shown to have harmful impacts on the cardiovascular system. Increased heartbeat and blood pressure have been linked to methamphetamine abuse[45,46]. In female rats exposed to methamphetamine, administration of 40 mg/kg of crocin with 40 mg/kg along with exercise for a 4-week withdrawal period, ameliorated the structural and inflammatory injuries in heart tissue[47]. In patients with breast cancer, the effect of crocin (tablets containing 12 mg, 3 times daily) against cardiotoxicity resulting from anthracycline was evaluated. The results showed that crocin prevented the reduction of left ventricular ejection fraction[48]. In another study, use of 30 mg of crocin for 8 weeks upregulated the gene expression of *SIRT1* and *AMPK* and downregulated the level of LOX1 and NF-κB[49].

5. Effect of crocin on the respiratory system

Asthma is a chronic inflammatory lung disease affecting individuals of all ages[50]. It is characterized by airway hyperresponsiveness, excessive mucus secretion, and airway remodeling[51]. It has been detected that amelioration of asthma symptoms can be a result of the inhibition of NF-κB signaling pathway, increased expression of nuclear factor-erythroid 2-related factor 2 (Nrf2) and heme oxygenase 1 (HO-1), and reduction of serum level of Ig E[52]. Ovalbumin is a protein found abundantly in the egg white, and it can cause hypersensitivity. It is broadly used to induce asthma in experimental studies[53]. In a model of ovalbumin-induced asthma, crocin, especially at 60 mg/kg, significantly suppressed ovalbumin-evoked lung hypersensitivity *via* decreasing the number of white blood cells, and the levels of IL-17, NF-κB, and Ig E, and upregulating the expression of Nrf2 and HO-1[54]. Aslani *et al*. reported that crocin mitigated lung injuries by declining T-bet/GATA-3 ratio, and downregulating miR-14a and miR-16a levels in ovalbumin-sensitized mice[55]. In a clinical trial, treatment with crocin at a dose of 15 mg twice daily for 12 weeks improved chronic obstructive pulmonary disease symptoms by reducing inflammatory cytokines including IL-6 and TNF-α[56].

High mobility group box 1 (HMGB1) is a secreted protein by immune cells in humans. It exerts its impacts through the Toll-like receptors and acts as a mediator in inflammatory responses resulting from endotoxemia and sepsis[57,58]. In rats exposed to 30 mg/kg of LPS, administration of 50 mg/kg of crocin for 9 days could reduce lung damage by suppressing the inflammatory reactions related to the HMGB1-TLR-4 signaling pathway[59]. Gao *et al*. examined the protective effect of crocin against caecal ligation and puncture-caused sepsis in lung, kidney, and liver tissues of mice. According to their findings, crocin modulated the activity of p38 MAPK/NF-κB/IκBα and Bcl-2/Bax pathways and mitigated the levels of IL-6 and TNF-α[60].

6. Effect of crocin on the gastrointestinal tract and liver

Intestinal ulcer is an inflammatory bowel disease that results in severe injury to mucosa and submucosa layers[61]. The main causes of intestinal ulcer are microbial infections and long-term consumption of non-steroidal anti-inflammatory drugs, including indomethacin[62,63]. In the study of Ghafarzadeh *et al*., intestinal ulcer was induced in rats by oral administration of 10 mg/kg of indomethacin. Treatment with crocin protected against indomethacin-caused intestinal ulcer *via* decreasing the levels of MDA, caspase 3, and TNF-α, and increasing the activity of SOD[64]. In acetic acid-induced ulcerative colitis, treatment with 20 mg/kg of crocin obviously downregulated expression of BAX, caspase 3/8/9, NF-κB, IL-1β, IL-6, and TNF-α and upregulated the levels of IL-4, IL-10, and BCL2 in rats, thereby improving colon injuries[65]. Cosgun *et al*. also elucidated the protective effects of 100 mg/kg of crocin against CCl_4-triggered intestinal damage. This positive impact of crocin was also associated with its antioxidant effects. In this research, a decreased level of oxidant indices, such as MDA, and an increased level of antioxidant parameters, such as GSH, in crocin-treated rats in comparison with the CCl_4 group were observed[66]. Methylglyoxal is an α-ketoaldehyde formed endogenously as a byproduct of the glycolytic pathway. Besides inducing diabetes, methylglyoxal can react with proteins and DNA and increase reactive oxygen species production[67]. It has been recognized that inflammation induced by the excessive accumulation of methylglyoxal causes hepatocyte injuries[68]. Radmehr *et al*. demonstrated that 60 mg/kg of crocin in combination with garlic acid (30 mg/kg) exerted protective impacts against methylglyoxal-induced liver damage by regulating the expression of NF-κB, TNF-α, HMGB1, and ATG7[69].

7. Effect of crocin on the urinary system

Diabetic nephropathy (DN) is a renal disturbance characterized by damage to the glomerular filtration barrier[70]. The regulation of blood glucose and blood pressure, and the use of anti-inflammatory and antioxidant agents, have outstanding effects in the treatment of DN[71]. Scientific evidence demonstrates that endoplasmic reticulum

Table 1. Effects of crocin on different systems.

Type of system	Dose	Type of study	Effects	Reference
Nervous	30 mg/kg	Animal	Improves anxiety-like behaviors, memory deficits, and synaptic plasticity	[12]
	160 mg/kg	Animal	Ameliorates learning and memory indices and anxiety	[13]
	40 mg/kg	Animal	Improves spatial memory, enhances the activity of PI3K/AKT signaling pathway, and decreases TNF-α, IL-1β and IL-6 levels	[17]
	10 mg/kg	Animal	Enhances sensory and motor activities and increases BDNF and NGF1 levels in the brain	[20]
	100 mg/kg	Animal	Alleviates motor disorders, diminishes the serum level of MDA, and increases the blood concentration of GPx and SOD	[21]
	15 mg/day	Human	Decreases the serum level of C-reactive protein	[22]
	30 mg/day	Human	Ameliorates movement activities and neuronal oxidative injuries	[23]
	100 mg/kg	Animal	Improves spatial learning and memory, inhibits lipid peroxidation, and downregulates the expression of caspase 3, TNF-α, and NF-κB in the brain	[25]
	10 and 50 mg/kg	Animal	Mitigates cognitive deficits, increases SOD activity, and reduces caspase 3	[27]
Cardiovascular	0.05, 0.075, and 0.1 mg/kg	Animal	Increases calcium concentration in cardiomyocytes and improves contractility of heart by modulating the activity of Na^+-Ca^{2+} exchanger and SERCA2a	[31]
	10 and 50 mg/kg	Animal	Alleviates MI-induced cardiac arrhythmia by upregulation of Cx43 expression	[34]
	100 and 200 mg//kg	Animal	Reduces inflammatory reaction by suppression of KBTBD7 expression	[37]
	4 and 12 mg/kg	Animal	Alleviates atherosclerosis by stimulating reverse cholesterol transporter and regulating the PPARγ/LXRs pathway	[41]
	40 mg/kg	Animal	Protects heart tissue by lowering MDA, TNF-α, and caspase 3 levels, elevating SOD, CAT, and GSH levels, and modifying lipid profile	[44]
	40 mg/kg	Animal	Ameliorates structural and inflammatory injuries in heart tissue	[47]
	12 mg/day	Human	Prevents the reduction of left ventricular ejection fraction	[48]
	30 mg/day	Human	Upregulates the gene expression of SIRT1 and AMPK and downregulates the level of LOX1 and NF-κB	[49]
Respiratory	60 mg/kg	Animal	Decreases the number of WBC, and the levels of IL-17, NF-κB, and Ig E, and upregulates Nrf2 and HO-1 expression	[54]
	50 and 100 mg/kg	Animal	Reduces T-bet/GATA-3 ratio, and downregulates miR-14a and miR-16a levels	[55]
	15 mg	Human	Improves chronic obstructive pulmonary disease symptoms by reducing inflammatory cytokines including IL-6 and TNF-α	[56]
	50 mg/kg	Animal	Suppresses HMGB1-TLR-4 signaling pathway-related inflammatory reactions	[59]
	50, 100, and 200 mg/kg	Animal	Modulates the activity of p38 MAPK/NF-κB/IκBα and Bcl-2/Bax pathways and causes a decline in the levels of IL-6 and TNF-α	[60]
Gastrointestinal	2.5, 10, and 40 mg/kg	Animal	Decreases MDA, caspase 3, and TNF-α levels, and increases SOD activity	[64]
	20 mg/kg	Animal	Downregulates BAX, caspase 3/8/9, NF-κB, IL-1β, IL-6 and TNF-α, and upregulates IL-4, IL-10 and BCL2	[65]
	100 mg/kg	Animal	Decreases oxidant indices, such as MDA, and increases antioxidant parameters such as GSH	[66]
	60 mg/kg	Animal	Regulates NF-κB, TNF-α, HMGB1, and ATG7 expression	[69]
Urinary	40 mg/kg	Animal	Reduces oxidant parameters such as MDA, increases antioxidant factors such as SOD, CAT, and GSH, and upregulates the Nrf2 and PI3K/AKT pathway	[74]
	100 mg/kg	Animal	Activates the Sirt1/Nrf2/HO-1 pathways	[75]
	50 mg/kg	Animal	Decreases TGF-β level	[77]
	10, 20, and 40 mg/kg	Animal	Augments antioxidant enzymes SOD and GSH, reduces MDA, upregulates CYP4A11 and phosphorylated PPARγ, and downregulates TGF-β and phosphorylated Smad2/3	[78]
	100 mg/kg	Animal	Attenuates iNOS, COX2, NF-κB and TNF-α expression	[81]
	12.5, 25, and 50 mg/kg	Animal	Reduces oxidant biomarkers such as MDA and elevates antioxidant capacity	[82]
	40 mg/kg	Animal	Modulates the levels of creatinine, blood urea nitrogen, MDA, and GSH	[83]
	15 mg/day	Human	Decreases the serum level of TGF-β and triglyceride	[84]

TNF-α: tumor necrosis factor alpha, IL: interleukin, BDNF: brain derived neurotrophic factor, NGF: nerve growth factor, MDA: malondialdehyde, GPx; glutathione peroxidase, SOD: superoxide dismutase, SERCA: sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase, MI: myocardial infarction, KBTBD: Kelch repeat and BTB domain-containing protein, PPARγ/LXRs: peroxisome proliferator-activated receptor γ/liver X receptors, CAT: catalase, GSH: glutathione, SIRT1: silent information regulator 1, AMPK: AMP activated protein kinase, LOX1: Lectin-like oxidized LDL receptor 1, NF-κB: nuclear factor kappa B, WBC: white blood cells, Nrf2: nuclear factor-erythroid 2-related factor 2, HO: heme oxygenase, T-bet: T-box expressed in T-cells, GATA: GATA-binding proteins, HMGB: high mobility group box, TLR: toll-like receptor, MAPK: mitogen-activated protein kinase, IκBα: inhibitor of κB alpha, PI3K: phosphoinositide 3-kinase, TGF-β: transforming growth factor beta, iNOS: inducible nitric oxide synthase, COX2: cyclooxygenase-2.

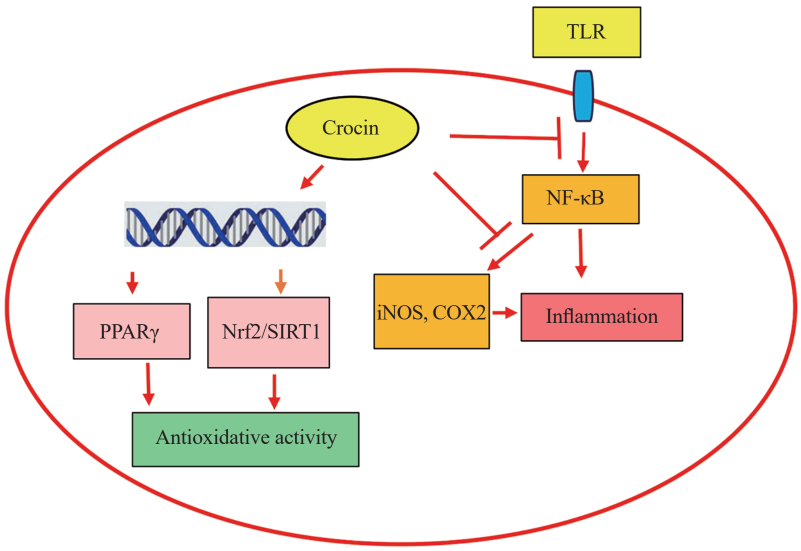

Figure 1. Molecular mechanisms of the therapeutic effects of crocin.

stress plays a major role in the development and progression of DN[72]. It has also been recognized that upregulation of Nrf2 and the PI3K/AKT pathway prevents endoplasmic reticulum stress-caused apoptosis[73]. In a mouse model of DN, receiving 40 mg/kg of crocin for two weeks ameliorated endoplasmic reticulum stress-evoked renal damage by reducing oxidant parameters such as MDA, increasing antioxidants such as SOD, CAT, and GSH, and activating the Nrf2 and PI3K/AKT pathway[74]. Administration with 100 mg/kg of crocin for 30 days also mitigated anti-Fx1A serum-induced nephropathy in rats by activation of the Sirt1/Nrf2/HO-1 pathway[75]. Increased transforming growth factor β (TGFβ) as a result of hyperglycemia has been considered a factor causing kidney dysfunction[76]. In streptozotocin-induced DN, 50 mg/kg of crocin decreased TGF-β level and improved kidney function in rats[77]. Chen *et al*. also reported that crocin at doses of 10, 20, and 40 mg/kg alleviated DN in mice by augmenting SOD and GSH activities and reducing MDA. In addition, Western blotting findings displayed that 40 mg/kg of crocin increased the expression of CYP4A11 and phosphorylated PPARγ, and decreased the expression of TGF-β and phosphorylated Smad2/3[78].

One of the side effects of some drugs, such as doxorubicin, is nephrotoxicity. Although the precise mechanisms of kidney damage caused by these compounds have not been recognized; however, oxidative stress has been suggested to be involved in this process[79,80]. Hussain *et al*. highlighted that crocin reduced doxorubicin-induced nephrotoxicity *via* downregulating the expressions of iNOS, COX2, NF-κB, and TNF-α[81]. Furthermore, crocin conferred protection against methotrexate-induced kidney injuries in rats by reducing MDA level and elevating antioxidant activities[82]. Rajabalizadeh *et al*. also confirmed the beneficial effect of crocin on colistin-caused kidney injury, as evidenced by modulation of the levels of creatinine, blood urea nitrogen, MDA, and GSH[83]. The results of a randomized clinical trial also demonstrated that the therapeutic effects of 15 mg/day of crocin for 90 days on patients with DN were associated with decreased serum level of TGF-β and triglyceride[84]. The effects of crocin on different systems are summarized in Table 1.

8. Conclusion

As indicated by the findings of this review, the antioxidant and anti-inflammatory properties of crocin play a critical role in the therapeutic effects of this herbal compound. Crocin modulates the activity of iNOS and COX2, and intracellular signaling pathways including PI3K/AKT, NF-κB, and PPARγ/LXRs pathways. Its beneficial effects are also associated with the increased expression of Nrf2, SIRT1, and Bcl2 and decreased levels of TNF-α, IL-1β, IL-6, TGF-β, Bax, and caspases (Figure 1). Nevertheless, more investigations are needed to verify its efficacy and safety.

Conflict of interest statement

Akbar Anaeigoudari is an editorial board member of this journal but has no role in the decision to publish this article. No potential conflict of interest relevant to this article was reported.

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Data availability statement

The data supporting the findings of this study are available from the corresponding author upon request.

Authors' contributions

AA programmed the study, collected data, and prepared the manuscript. FM assisted in preparing the data and revised the manuscript.

References

[1] Heydari M, Zare M, Badie MR, Watson RR, Talebnejad MR, Afarid M. Crocin as a vision supplement. *Clin Exp Optom* 2023; **106**(3): 249-256.

[2] Anaeigoudari A. A narrative review of protective effects of natural compounds against lipopolysaccharide-induced injuries. *Food Sci Nut* 2025; **13**(2): e70026.

[3] Chen X, Huang J, Lv Y, Chen Y, Rao J. Crocin exhibits an antihypertensive effect in a rat model of gestational hypertension and activates the Nrf-2/HO-1 signaling pathway. *Hypertens Res* 2021; **44**(6): 642-650.

[4] Rahimi G, Shams S, Aslani MR. Effects of crocin supplementation on inflammatory markers, lipid profiles, insulin and cardioprotective indices in women with PCOS: A randomized, double-blind, placebo-controlled trial. *Phytother Res* 2022; **36**(6): 2605-2615.

[5] Kakhki S, Abbaszade-Cheragheali A, Tafti SP, Feizabadi AS, Ahmadi-Soleimani SM, Beheshti F. Oral administration of crocin reverses memory loss induced by ethanol and nicotine abstinence in adolescent male rats. *Neurosci Lett* 2025; **846** 138077.

[6] Asdaq SMB, Mannasaheb BA, Orfali R, Shaikh IA, Alshehri A, Alghamdi A, et al. Antidiabetic and antioxidant potential of crocin in high-fat diet plus streptozotocin-induced type-2 diabetic rats. *Int J Immunopathol Pharmacol* 2024; **38**. doi: 10.1177/03946320231220178.

[7] Hong R, Chen B, Wu H, Ding J. Crocin facilitates osteogenesis and angiogenesis by moderating oxidative stress and ferroptosis *via* Nrf2/GPX4 pathway. *Tissue Cell* 2025; **93**: 102675.

[8] Hosseini SS, Nazifi P, Amini M, Zargari F, Yari AH, Baradaran B, et al. Crocin suppresses colorectal cancer cell proliferation by regulating miR-143/145 and KRAS/RREB1 pathways. *Anticancer Agents Med Chem* 2023; **23**(17): 1916-1923.

[9] Farahi A, Abedini MR, Javdani H, Arzi L, Chamani E, Farhoudi R, et al. Crocin and Metformin suppress metastatic breast cancer progression *via* VEGF and MMP9 downregulations: *In vitro* and *in vivo* studies. *Mol Cell Biochem* 2021; **476**(9): 3341-3351.

[10] Xu X, Xuan S, Chen S, Liu D, Xiao Q, Tu J. Increased excitatory amino acid transporter 2 levels in basolateral amygdala astrocytes mediate chronic stress-induced anxiety-like behavior. *Neural Regen Res* 2025; **20**(6): 1721-1734.

[11] Buenrostro-Jáuregui MH, Muñóz-Sánchez S, Rojas-Hernández J, Alonso-Orozco AI, Vega-Flores G, Tapia-de-Jesús A, et al. A comprehensive overview of stress, resilience, and neuroplasticity mechanisms. *Int J Mol Sci* 2025; **26**(7): 3028.

[12] Jahromi GP, Jangravi Z, Hadipour M, Shirvani H, Afarinesh MR, Meftahi GH. Comparative effects of the alcoholic extract of *Terminalia chebula* and crocin on stress-induced anxiety-like behavior and memory impairment in male rats. *Acta Neurobiol Exp* 2023; **83**(2): 179-193.

[13] Khodadadi M, Jahromi GP, Meftahi GH, Khodadadi H, Hadipour M, Ezami M. Crocin nano-chitosan-coated compound mitigates hippocampal blood-brain barrier disruption, anxiety, and cognitive deficits in chronic immobilization stress-induced rats. *Heliyon* 2024; **10**(20): e39203.

[14] Shah S, Jain H. Microglia-associated neuroinflammation in Alzheimer's disease and its therapeutic potential. *Neuroglia* 2024; **5**(4): 452-466.

[15] Anaeigoudari A, Norouzi F, Abareshi A, Beheshti F, Aaghaei A, Shafei MN, et al. Protective effects of *Nigella sativa* on synaptic plasticity impairment induced by lipopolysaccharide. *Vet Res Forum* 2018; **9**(1): 27-33.

[16] Shabab T, Khanabdali R, Moghadamtousi SZ, Kadir HA, Mohan G. Neuroinflammation pathways: A general review. *Int J Neurosci* 2017; **127**(7): 624-633.

[17] Su W, Wang Y, Shao S, Ye X. Crocin ameliorates neuroinflammation and cognitive impairment in mice with Alzheimer's disease by activating PI3K/AKT pathway. *Brain Behav* 2024; **14**(5): e3503.

[18] Okutan B, Frederiksen JL, Houen G, Sellebjerg F, Kyllesbech C, Magyari M, et al. Subcortical plaques and inflammation reflect cortical and meningeal pathologies in progressive multiple sclerosis. *Brain Pathol* 2025; **35**(3): e13314.

[19] Portaccio E, Amato MP. Cognitive impairment in multiple sclerosis: An update on assessment and management. *Neuro Sci* 2022; **3**(4): 667-676.

[20] Fatemi R, Moghaddam HF, Farbod Y, Bigtashkhani R. Effects of crocin on brain neurotrophins, cognition, balance and pain in toxic-induced demyelination model. *Acta Neurol Taiwan* 2024; **33**(2): 47-54.

[21] Tashakori A, Hassanpour S, Vazir B. Protective effect of crocin on cuprizone-induced model of multiple sclerosis in mice. *Naunyn Schmiedebergs Arch Pharmacol* 2023; **396**(8): 1713-1725.

[22] Kouchaki E, Rafiei H, Ghaderi A, Azadchehr MJ, Safa F, Omidian K, et al. Effects of crocin on inflammatory biomarkers and mental health status in patients with multiple sclerosis: A randomized, double-blinded clinical trial. *Mult Scler Relat Disord* 2024; **83**. doi: 10.1016/j.msard.2024.105454.

[23] Mohammad Soleymani S, Assarzadegan F, Habibi SAH, Mahboubi A, Esmaily H. The effect of crocin on movement disorders and oxidative DNA damage in Parkinson's disease: Insights from a randomized controlled trial. *Parkinsonism Relat Disord* 2024; **126**. doi: 10.1016/j.parkreldis.2024.107051.

[24] Wang Y, Du P, Jiang D. Rigosertib inhibits MEK1-ERK pathway and alleviates lipopolysaccharide-induced sepsis. *Immun Inflamm Dis* 2021; **9**(3): 991-999.

[25] Dastan M, Rajaei Z, Sharifi M, Salehi H. Crocin improves cognitive impairment in LPS-treated rats by anti-apoptotic, anti-inflammatory and antioxidant activities. *Mol Neurobiol* 2025; **62**(5): 5804-5815.

[26] Chang W, An J, Seol GH, Han SH, Yee J, Min SS. *Trans*-anethole alleviates trimethyltin chloride-induced impairments in long-term potentiation. *Pharmaceutics* 2022; **14**(7): 1422.

[27] Ghofrani S, Joghataei MT, Afshin-Majd S, Baluchnejadmojarad T,

Roghani M. Crocin, a bioactive constituent of *Crocus sativus*, alleviates trimethyltin-induced cognitive deficits through down-regulation of hippocampal apoptosis and oxidative stress. *J Basic Clin Pathophysiol* 2022; **10**(1): 38-44.

[28]Szymczak A, Skwarek-Dziekanowska A, Sobieszek G, Małecka-Massalska T, Powrózek T. Comparison of the clinical value of inflammatory blood biomarkers in relation to disease severity and survival in chronic heart failure. *Int J Cardiol* 2025; **429**: 133165.

[29]Kona'atul H, Nani M, Adriyan P. Diet and the gut microbiota profiles in individuals at risk of chronic heart failure–A review on the Asian population. *Asia Pac J Clin Nutr* 2025; **34**(2): 141-152.

[30]Pan LP, Zhu L, Wang BX, Li YQ, Gao L, Zhao HH. Exploring natural therapy for chronic heart failure: Experience in traditional Chinese medicine treatment before 2022. *Front Med* 2025; **12**: 1522163.

[31]Hu Y, Yang J, Pang Q, Zhang P, Liu K. Protective effect of crocin on chronic heart failure and its mechanism of action. *Trop J Pharm Res* 2023; **22**(1): 113-120.

[32]Tribulova N, Knezl V, Okruhlicova L, Slezak J. Myocardial gap junctions: Targets for novel approaches in the prevention of life-threatening cardiac arrhythmias. *Physiol Res* 2008; **57**: S1-S13.

[33]Zhou P, Yang X, Yang D, Jiang X, Wang WE, Yue R, et al. Integrin-linked kinase activation prevents ventricular arrhythmias induced by ischemia/reperfusion *via* inhibition of connexin 43 remodeling. *J Cardiovasc Transl Res* 2021; **14**: 610-618.

[34]Li H, Li J, Wang J, Afzal O, Altamimi AS, Nasar Mir Najib Ullah S, et al. Analysis of anti-arrhythmic impacts of crocin through estimation of expression of Cx43 in myocardial infarction using a rat animal model. *ACS Omega* 2022; **7**(42): 37164-37169.

[35]Hu J, Yuan W, Tang M, Wang Y, Fan X, Mo X, et al. KBTBD7, a novel human BTB-kelch protein, activates transcriptional activities of SRE and AP-1. *BMB Rep* 2010; **43**(1): 17-22.

[36]Shen W, Zhang X, Tang M, Chen W, Wang Y, Zhou H. Targeting of ubiquitination and degradation of KLF15 by E3 ubiquitin ligase KBTBD7 regulates LPS-induced septic brain injury in microglia. *Exp Cell Res* 2024; **443**(1): 114317.

[37]Yuan C, Chen Z, Zhou Q. Crocin inhibits KBTBD7 to prevent excessive inflammation and cardiac dysfunction following myocardial infarction. *Mol Med Rep* 2022; **27**(1): 20. doi: 10.3892/mmr.2022.12907.

[38]Hua S, Sun L, Zhang H, Shiu C, Zhang S, Zhu Y, et al. Yiqi Wenyang decoction protects against the development of atherosclerosis by inhibiting vascular inflammation. *Pharm Biol* 2025; **63**(1): 264-274.

[39]Biccirè FG, Mastroianni F, Celeski M, Gatto L, Prati F. Reducing the risk of heart attack: The key role of lipid profiling and atherosclerosis imaging. *Eur Heart J Suppl* 2025; **27**: 22-24.

[40]Zhang Z, Zhai L, Lu J, Sun S, Wang D, Zhao D, et al. Shen-Hong-Tong-Luo Formula attenuates macrophage inflammation and lipid accumulation through the activation of the PPAR-γ/LXR-α/ABCA1 pathway. *Oxid Med Cell Longev* 2020; **2020**(1): 3426925.

[41]Zhang F, Liu P, He Z, Zhang L, He X, Liu F, et al. Crocin ameliorates atherosclerosis by promoting the reverse cholesterol transport and inhibiting the foam cell formation *via* regulating PPARγ/LXR-α. *Cell Cycle* 2022; **21**(2): 202-218.

[42]Gu X, Zhao L, Ye J, Chen L, Sui C, Li B, et al. 1,25 $(OH)_2D_3$ ameliorates doxorubicin-induced cardiomyopathy by inhibiting the NLRP3 inflammasome and oxidative stress. *Exp Ther Med* 2023; **26**(3): 413.

[43]Kang S, Li H, Li M, Zhao Y, Pang J, Dan J, et al. Erianin alleviates doxorubicin-induced cardiotoxicity by activating the Keap1-Nrf2 signaling pathway. *Phytomedicine* 2025; **141**: 156684.

[44]Abdulkareem Aljumaily SA, Demir M, Elbe H, Yigitturk G, Bicer Y, Altinoz E. Antioxidant, anti-inflammatory, and anti-apoptotic effects of crocin against doxorubicin-induced myocardial toxicity in rats. *Environ Sci Pollut Res Int* 2021; **28**: 65802-65813.

[45]Tobolski J, Sawyer DB, Song SJ, Afari ME. Cardiovascular disease associated with methamphetamine use: A review. *Heart Fail Rev* 2022; **27**(6): 2059-2065.

[46]Fang S, Huang C, Huang S, Shao Y. Associations and relative risks of pulmonary hypertension and lung diseases in individuals with methamphetamine use disorder. *Pulmonology* 2024; **30**(6): 577-585.

[47]Ziaolhagh SJ, Rajabi S, Nosrati Z. Examining the cardioprotective effects of aerobic exercise combined with crocin or berberine on methamphetamine-induced heart damage in female Rats. *Int J High Risk Behav Addict* 2024; **13**(3): e147435.

[48]Li X, Su X, Liang W, Wang L, Yuan C, Xu J, et al. Cardioprotective effect of crocin in patients with breast cancer receiving anthracycline-based chemotherapy: A randomized, double-blind, placebo-controlled study. *Pharmacol Res* 2025; **213**. doi: 10.1016/j.phrs.2025.107630.

[49]Abedimanesh N, Motlagh B, Abedimanesh S, Bathaie SZ, Separham A, Ostadrahimi A. Effects of crocin and saffron aqueous extract on gene expression of SIRT1, AMPK, LOX1, NF-κB, and MCP-1 in patients with coronary artery disease: A randomized placebo-controlled clinical trial. *Phytother Res* 2020; **34**(5): 1114-1122.

[50]Liu J, Li Z, Li Z, Wang A, Liao X, Liu Z, et al. Fudosteine attenuates lung inflammation in mice with PM2.5-induced asthma exacerbation by inhibiting pyroptosis *via* the NLRP3/caspase-1/GSDMD pathway. *Toxicol Appl Pharmacol* 2025; **499**. doi: 10.1016/j.taap.2025.117346.

[51]Chen MC, Tai JW, Wu CJ. Induction of airway hypersensitivity to ovalbumin and dust mite allergens as mouse models of allergic asthma. *Methods Mol Biol* 2021; **2223**: 101-114.

[52]Dong Y, Zou YZ, Li T, Sun JH, Li H, Zhuang WY, et al. Schisandrol A alleviates allergic asthma in mice *via* regulating the NF-κB/IκBα and Nrf2/HO-1 signaling pathways. *J Med Food* 2025; **28**(1): 28-37.

[53]Kim SK, Do JW, Lee SK, Park JH, Kim JH, Lim HB. Inhibitory effects of *Phellodendri cortex* against airway inflammation and hyperresponsiveness in ovalbumin-induced murine asthma model. *Molecules* 2025; **30**(8): 1795.

[54]Jeddi F, Zahertar S, Bordbar A, Salimnejad R, Ghobadi H, Aslani MR. Crocin from saffron ameliorates allergic airway inflammation through NF-κB, IL-17, and Nrf2/HO-1 signaling pathways in mice. *Iran J Basic Med Sci* 2024; **27**(12): 1624-1631.

[55]Aslani MR, Jafari Z, Rahbarghazi R, Rezaie J, Delkhosh A, Ahmadi M. Effects of crocin on T-bet/GATA-3 ratio, and miR-146a and miR-106a expression levels in lung tissue of ovalbumin-sensitized mice. *Iran J Basic Med Sci* 2022; **25**(10): 1267-1274.

[56]Aslani MR, Abdollahi N, Matin S, Zakeri A, Ghobadi H. Effect of crocin of *Crocus sativus* L. on serum inflammatory markers (IL-6 and TNF-α) in chronic obstructive pulmonary disease patients: A randomised, double-

blind, placebo-controlled trial. *Br J Nutr* 2023; **130**(3): 446-453.

[57]Wang Z, Yang X, Wang X, Liang F, Tang Y. Glycyrrhizin attenuates caspase-11-dependent immune responses and coagulopathy by targeting high mobility group box 1. *Int Immunopharmacol* 2022; **107**: 108713.

[58]Bae JS. Role of high mobility group box 1 in inflammatory disease: Focus on sepsis. *Arch Pharm Res* 2012; **35**: 1511-1523.

[59]Ceylan T, Akin AT, Kaymak E, Varinli S, Toluk A. Crocin suppresses inflammatory response in LPS-induced acute lung injury (ALI) *via* regulation of HMGB1/TLR4 inflammation pathway. *J Basic Clin Health Sci* 2024; **8**: 271-278.

[60]Gao J, Zhao F, Yi S, Li S, Zhu A, Tang Y, et al. Protective role of crocin against sepsis-induced injury in the liver, kidney and lungs *via* inhibition of p38 MAPK/NF-κB and Bax/Bcl-2 signalling pathways. *Pharm Biol* 2022; **60**(1): 543-552.

[61]Zhou J, Zhu F, Liang H, Sun L. Network pharmacology and experimental validation reveal Sishen Pill's efficacy in treating NSAID-induced small intestinal lcers. *Drug Des Devel Ther* 2025; **19**: 2035-2050.

[62]Satoh H, Takeuchi K. Management of NSAID/aspirin-induced small intestinal damage by GI-sparing NSAIDs, anti-ulcer drugs and food constituents. *Curr Med Chem* 2012; **19**(1): 82-89.

[63]Jin LX, Fang YP, Xia CM, Cai TW, Li QQ, Wang YY, et al. *Helicobacter pylori* infection alters gastric microbiota structure and biological functions in patients with gastric ulcer or duodenal ulcer. *World J Gastroenterol* 2024; **30**(24): 3076-3085.

[64]Ghafarzadeh S, Hobbenaghi R, Tamaddonfard E, Farshid AA, Imani M. Crocin exerts improving effects on indomethacin-induced small intestinal ulcer by antioxidant, anti-inflammatory and anti-apoptotic mechanisms. *Vet Res Forum* 2019; **10**(4): 277-284.

[65]Albalawi GA, Albalawi MZ, Alsubaie KT, Albalawi AZ, Elewa MA, Hashem KS, et al. Curative effects of crocin in ulcerative colitis *via* modulating apoptosis and inflammation. *Int Immunopharmacol* 2023; **118**: 110138.

[66]Cosgun BE, Erdeml ME, Gul M, Gul S, Bag HG, Aksungur Z, et al. Crocin protects intestine tissue against carbon tetrachloride-mediated oxidative stress in rats. *Gen Physiol Biophys* 2018; **37**(4): 399-409.

[67]Zhu H, Wang W, Zhu J, Chen X, Wang J, Wang J, et al. Methylglyoxal deteriorates macrophage efferocytosis in diabetic wounds through ROS-induced ubiquitination degradation of KLF4. *Free Radic Biol Med* 2025; **231**: 23-37.

[68]Wang WC, Chou CK, Chuang MC, Li YC, Lee JA. Elevated levels of liver methylglyoxal and *D*-lactate in early-stage hepatitis in rats. *Biomed Chromatogr* 2018; **32**(2): e4039.

[69]Radmehr V, Mojadami S, Ahangarpour A, Mard SA. Protective effects of crocin and gallic acid on the liver damage induced by methylglyoxal in male mice: Role of inflammatory factors. *Gastroenterol Hepatol Bed Bench* 2023; **16**(1): 499-508.

[70]Wang Y, He W, Ren P, Zhao L, Zheng D, Jin J. Carthamin yellow-loaded glycyrrhetinic acid liposomes alleviate interstitial fibrosis in diabetic nephropathy. *Ren Fail* 2025; **47**(1): 2459356.

[71]Gaikwad AB, Hajare AD, Kulkarni H, Bhadange R. Combination of α-Klotho and telmisartan attenuates diabetic kidney disease *via* mitigating EMT, inflammation and apoptosis. *Biochem Biophys Res Commun* 2025; **760**: 151711.

[72]Fan Y, Lee K, Wang N, He JC. The role of endoplasmic reticulum stress in diabetic nephropathy. *Curr Diab Rep* 2017; **17**: 1-7.

[73]Zhang C, Wang H, Chan GC, Zhou Y, Lai X, Lian M. Extracellular vesicles derived from human umbilical cord mesenchymal stromal cells protect cardiac cells against hypoxia/reoxygenation injury by inhibiting endoplasmic reticulum stress *via* activation of the PI3K/Akt pathway. *Cell Transplant* 2020; **29**. doi: 10.1177/0963689720945677.

[74]Wang G, Deng J, Hua Z. Crocin protects against endoplasmic reticulum stress-related tubular injury in diabetic nephropathy *via* the activation of the PI3K/AKT/Nrf2 pathway. *Iran J Basic Med Sci* 2024; **27**(4): 439-446.

[75]Liu H, Cheng H, Wang H, Wang Q, Yuan J. Crocin improves the renal autophagy in rat experimental membranous nephropathy *via* regulating the SIRT1/Nrf2/HO-1 signaling pathway. *Ren Fail* 2023; **45**(2): 2253924.

[76]Hong Q, Kim H, Cai GY, Chen XM, He JC, Lee K. Modulation of TGF-β signaling new approaches toward kidney disease and fibrosis therapy. *Int J Biol Sci* 2025; **21**(4): 1649-1665.

[77]Mohammadi Y, Zangooei M, Zardast M, Mamashli M, Farimani AR. The effect of crocin and losartan on TGF-β gene expression and histopathology of kidney tissue in a rat model of diabetic nephropathy. *Avicenna J Phytomed* 2023; **13**(2): 189-199.

[78]Chen W, Su J, Liu Y, Gao T, Ji X, Li H, et al. Crocin ameliorates diabetic nephropathy through regulating metabolism, CYP4A11/PPARγ, and TGF-β/Smad pathways in mice. *Curr Drug Metab* 2023; **24**(10): 709-722.

[79]Wang L, Wei C, Jing J, Shao M, Wang Z, Wen B, et al. The effects of polyphenols on doxorubicin-induced nephrotoxicity by modulating inflammatory cytokines, apoptosis, oxidative stress, and oxidative DNA damage. *Phytother Res* 2025; **39**(5): 2147-2164.

[80]Azman PD, Yildirim S, Sengu E, Warda M, Tekin S, Aykurt F, et al. Protective effects of naringin against oxidative stress, inflammation, apoptosis, and DNA damage in rats with doxorubicin-induced hepatotoxicity. *Asian Pac J Trop Biomed* 2025; **15**(7): 285-295.

[81]Hussain MA, Abogresha NM, AbdelKader G, Hassan R, Abdelaziz EZ, Greish SM. Antioxidant and anti-inflammatory effects of crocin ameliorate doxorubicin-induced nephrotoxicity in rats. *Oxid Med Cell Longev* 2021; **2021**(1): 8841726.

[82]Jalili C, Ghanbari A, Roshankhah S, Salahshoor MR. Toxic effects of methotrexate on rat kidney recovered by crocin as a consequence of antioxidant activity and lipid peroxidation prevention. *Iran Biomed J* 2019; **24**(1): 39-46.

[83]Rajabalizadeh R, Rahbardar MG, Razavi BM, Hosseinzadeh H. Renoprotective effects of crocin against colistin-induced nephrotoxicity in a rat model. *Iran J Basic Med Sci* 2024; **27**(2): 151-156.

[84]Jaafarinia A, Kafami B, Sahebnasagh A, Saghafi F. Evaluation of therapeutic effects of crocin in attenuating the progression of diabetic nephropathy: A preliminary randomized triple-blind placebo-controlled trial. *BMC Complement Med Ther* 2022; **22**(1): 262.

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