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Review

An evaluation on potential anti-oxidant and anti-inflammatory effects of Crocin

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ABSTRACT

Crocin, an active ingredient derived from saffron, is one of the herbal components that has recently been considered by researchers. Crocin has been shown to have many anti-inflammatory and antioxidant properties, and therefore can be used to treat various diseases. It has been shown that Crocin has a positive effect on the prevention and treatment of cardiovascular disease, cancer, diabetes, and kidney disease. In addition, the role of this substance in COVID-19 pandemic has been identified. In this review article, we tried to have a comprehensive review of the antioxidant and anti-inflammatory effects of Crocin in different diseases and different tissues. In conclusion, Crocin may be helpful in pathological conditions that are associated with inflammation and oxidative stress.

1. Introduction

Reactive oxygen species (ROS) which characterize as the chemically reactive molecules for example NO, H_2O_2, and O_2^-, are natural products of cellular metabolism, which are capable of changing redox balance [1, 2]. ROS along with inflammation are considered two important factors in pathogenicity of human diseases. ROSs perform various physiological roles in gene expression, signaling processes and cellular defense against extrinsic invader pathogens. Oxidative stress occupies an axial role in development of several pathophysiological states [3]. This pathological condition occurs when free radicals are overproduced and overcome intrinsic antioxidant defense system [4]. The large body of evidence demonstrates that ROS exert undesirable effects in different tissues and it is clear that ROS have undeniable role in generation and progression of renal, gastrointestinal, hepatitis, neurodegenerative, cardiovascular, and inflammatory disease [5–7].

Inflammation is a defense process protected against diseases and external factors such as bacteria, viruses, etc. Mitochondria, as the main organ of energy production, play a major role in causing inflammation and oxidative stress [8]. Mitochondria is an important part of innate immunity and inflammation and derangement of mitochondria can be considered a critical pathogenic tool of several diseases categorized by chronic inflammation, including neurodegenerative diseases, cancer, rheumatoid and metabolic disorders [9]. Targeting the process of inflammation and oxidative stress can be effective in reducing severity and incidence of diseases. Although chemical drugs are widely used to

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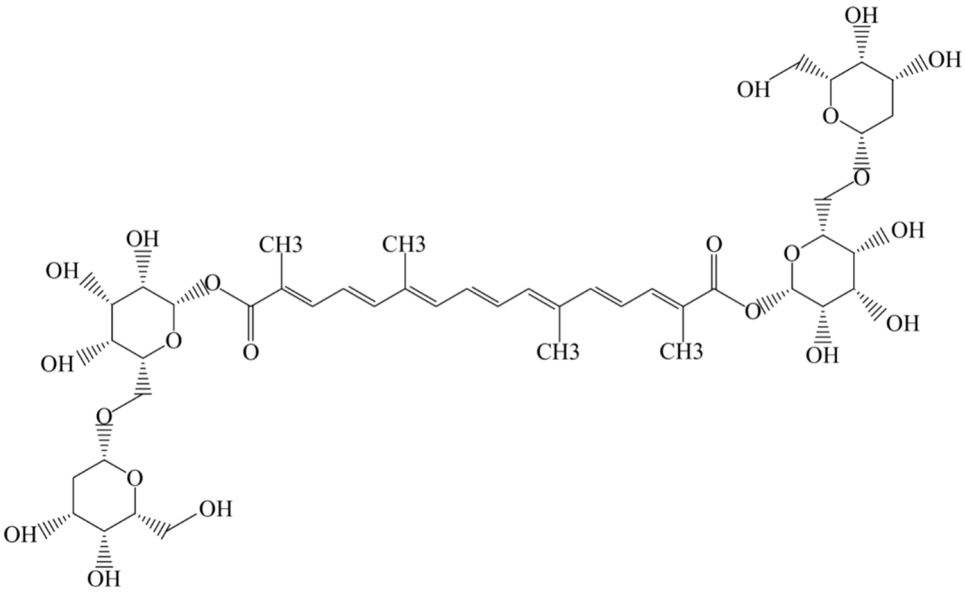

Fig. 1. Chemical structure of Crocin. Crocin is a water-soluble carotenoid isolated from *Crocus sativus* (saffron).

treat many diseases, a large body of evidence suggests that medicinal plants possess numerous therapeutic effects in various disorders due to their low toxicity and relatively strong efficacy, are suitable candidate and helpful strategy in front of various diseases [10–14]. For example, the positive effects of phenolic compounds, flavonoids such as Quercetin, Carotenoids and Alkaloids (include Crocin, Capsaicin) and ginger extract in liver cancer were approved by several studies [15,16]. In addition, the positive effects of herbal agents on the COVID-19 pandemic have been proven. In this regard, compound from herbal food of *Rhizoma Polygonati* may have potential therapeutic effect on Covid19 [17].

Saffron (*Crocus sativus L.*), a member of *Iridaceae* family [18], is cultivating in various countries for example India, Spain, Greece, China, Italy, Azerbaijan, Turkey, and Iran [19]. There is a growing interest in the isolated components of saffron because of their antioxidant and anti-inflammatory functions on human health through the following mechanisms: lipid peroxidation reduction, diazinon (DZN) inhibition, inflammatory cytokines and neuronal damage markers reductions due to its free radical scavenging activity [20]. According to the studies, the most bioactive compounds of saffron are *safranal, crocetin, picroCrocin,* and *Crocin* [21,22]. There are four sorts of *Crocin*, while the most of the *Crocins*, except *Crocin-1*, are found in cis-trans isomeric forms [23]. A great number of studies have revealed that Crocin possesses anti-oxidant, anti- inflammatory [24], renoprotective [25], anti-atherosclerotic [26], antidepressant [27], anti-platelet aggregation [28], and anti-cancer properties [7,29]. Crocin by scavenging the free radicals is capable of protecting the cells against oxidative stress damages. It is interesting to note that, Crocin by alteration in the enzyme activity and cellular oxidative defense system translation level for example: glutathione S-transferase (GST), glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT) makes a contribution to cell protection in front of ROS [30]. Endoplasmic reticulum (ER) maintains an axial role in protection of the cells in stress conditions and although, any changes in the mRNA expression level of the ER stressors including XBP-1/s (X-Box Binding Protein 1), BiP (Binding immunoglobulin protein), PERK (protein kinase R-like endoplasmic reticulum kinase), and CHOP (C/EBP homologous protein) have function in many stress-related diseases, for example Alzheimer Disease (ADs) and cancers. Crocin through promoting the ER enzymes' mRNA expression levels makes a contribution to the ER inducing and subsequently oxidative stress elements reduction [31,32]. Additionally, releasing of ROS species along with pro-inflammatory molecules production and transportation in to all tissues make a contribution to inflammatory disorders and as mentioned above, Crocin exerts an anti-inflammatory effects by scavenging the free radicals via modulating the oxidative stress defense system [33].

Moreover, the combination of nanoparticles and herbal agents is also very important in today's research. In this regard, Crocin-coated magnetite nanoparticles led to a substantial suppression of hepatocellular growth as compared to control or those treated with free Crocin or uncoated magnetite nanoparticles [34]. In this review, we evaluated the potential anti-oxidant and anti-inflammatory effects of Crocin in cancers and inflammatory disorders.

2. Chemistry of Crocin

Crocin (Fig. 1), a water-soluble carotenoid isolated from *Crocus sativus* (saffron) and *Gardenia jasminoides*, is the main pigment of saffron and gives red color crystals [10,35]. Comparative studies have demonstrated that Crocin possesses higher radical scavenging activity and anti-oxidant potential comparing to gallic acid, ascorbic acid and kaempferol [36,37]. The main free radical-detoxifying role of Crocin is due to the hydroxyl and glucose moieties as potential electron donors which react with free radicals and provide the essential anti-oxidant capacity [36].

Crocin is synthesized from the esterification of disaccharide gentiobiose and the dicarboxylic acid crocetin and is referred to a group of hydrophilic carotenoids including monoglycosyl or diglycosyl polyene esters of crocetin. The biosynthesis of Crocin occurs during zeaxanthin oxidation pathway in which Zeaxanthin Cleavage Dioxygenase (ZCD)/ Carotenoid Cleavage Dioxygenase 2 (CCD2) cleave zeaxanthin at 7,8 and 7',8' double bands into hydroxyl 3-OH-β-cyclocytral and crocetin dialdehyde. Crocetin dialdehyde forms crocetin by aldehyde dehydrogenase enzyme (ALDH) and then, UDP-glucosyltransferases convert crocetin to crocetin glycosides (Crocins). Glucosylation of crocetin improves water solubility and stability of the crocetin glycosides which is essential for their pharmacological properties [38,39].

When Crocin is orally consumed, it is hydrolyzed to deglycosylated trans-crocetin (the bio-active form of saffron) in gastrointestinal tract by enterocytes and gut microbiota [28,40]. After deglycosylation process, crocetin is rapidly absorbed via the portal vein to circulatory system and meet a plasmatic pick of concentration. On the contrary, intravenous administration of Crocin did not increase the level of crocetin in plasma, indicating the importance of gastrointestinal deglycosylation of Crocin

[41–43]. In line with previous findings, Zhang et al., revealed that oral administration of Crocin gives a higher plasmatic level of crocetin comparing to that of crocetin, suggesting the higher pharmacological value of Crocin in oral administration than crocetin [40]. Although, Crocin has a lower dissolution rate demanding different strategies to improve its bioavailability as a biologically active substance [44].

Crocin has been proved to be safe in lower doses (e.g. 20 mg/day, one month) [45], however Talaei et al., reported mild side effects such as menometrorrhagia, dyspnea and agitation following oral administration of 30 mg/day Crocin [46].

3. Effects of crocin in oxidative condition

In oxidative stress, the relative amount of ROS exceeds the antioxidant capacity, resulting in harmful effects on cellular components such as nucleic acids, proteins and cellular structures. This subsequently leads to various diseases and malignancies such as cardiovascular disease, neurodegenerative disease, metabolic disorders and cancers [47–53].

Various pharmacological agents are being used to enhance the antioxidant defense system [54–56]. Numerous studies have shown various pharmacological actions of Crocin including anti-oxidant and anti-inflammatory effects [35,57–59]. Crocin modulates oxidative stress mostly by scavenging free radicals and stimulating the expression of anti-oxidant enzymes including SOD, GPx, GST, and CAT and reduction of malonyldialdehyde (MDA) and peroxidized membrane lipids [35,58,60]. In streptozotocin-induced diabetic rats, there was an increase in ROS level and a reduction in the enzymatic activity of catalase, SOD and GPx that resulted in nephropathy, retinopathy, liver and pancreas dysfunction and coronary heart disease [61]. Studies have shown that using natural antioxidant agents such as Crocin modulates the oxidative stress-induced malfunctions [26–28]. Moreover, Li et al., showed that Crocin improved mitochondrial dysfunction by down-regulation of ROS-induced KCa3.1 via GPx1/ROS/KCa3.1 signaling pathways in the endothelium, leading to reduced production of ROS and endothelial dysfunction in diabetes [62]. Crocin could increase expression levels of SOD and CAT in streptozotocin-induced diabetic rats [63]. Additionally, radical-neutralizing role of Crocin leads to its anti-inflammatory effects by decreasing the lipid peroxidation and inflammatory cytokines, and inhibition of DZN [10]. Crocin also modulated doxorubicin-induced nephrotoxicity in rats by decreasing the expression of COX2, iNOS, TNFα via down-regulation of NF-κB [64]. Furthermore, Crocin modulated biochemical and histological changes in Bleomycin-treated rats, suggesting the protective role of Crocin against idiopathic pulmonary fibrosis [65]. In another study, Crocin exerted cardio-protective effect in doxorubicin-treated rats by ameliorating OS indices such as total oxidant status and MDA [59]. Jalili et al., reported that Crocin protected kidneys against MTX-induced renal damage in rats by suppressing the activity of NO via up-regulation of HO-1 and calmodulin/calcium-dependent protein kinase-4, suppressing the proteins and lipids peroxidation, increasing glutathione and antioxidant capacity, and regulating the inflammatory pathways [66]. Moreover, Crocin reduced ROS levels by increasing SOD and decreasing DNA breakage, and improving sperm membrane integrity in frozen-thawed buffalo sperm [67]. In oxidant condition, Crocin suppressed intracellular ROS production and elevated total antioxidant activity in H9C2 cells [68]. Also, it has been shown that Crocin exerts therapeutic potential against oxidative stress-associated skeletal muscle diseases [69]. Crocin, also increased GSH levels and suppressed the activation of JNK pathway, preventing the synthesis of serum/glucose deprivation-induced ceramide as a mediator in neuronal cell death [60]. Dianat et al., showed that Crocin protects rats against monocrotaline-induced pulmonary arterial hypertension by regulation of OXR1 signaling pathway [70]. Furthermore, Crocin improved arsenic trioxide-induced cardiotoxicity by regulation of Keap1-Nrf2/HO-1 signal transduction pathway [71].

Cells possess several antioxidant systems to create a balance between oxidants and antioxidants either by directly decreasing the formation of oxidants (e.g. ROS/RNS) and detoxifying the reactive metabolites, or by indirectly regulating the antioxidant defense systems [72]. Two main mechanism of actions of Crocin in scavenging free radicals are: 1) hydrogen atom transfer (HAT), and 2) single electron transfer. In HAT mechanism, Crocin deactivates free radicals by transferring hydrogen atom to free radicals. In another mechanism, SET, Crocin neutralizes free radicals by donating an electron to free radicals [73]. According to Ochiai et al., Crocin showed a higher anti-oxidative capacity than α-tocopherol [60,74]. The anti-oxidant role of Crocin has been demonstrated in several tissues of body such as kidney, spleen, liver, pancreas, brain, muscle cells, joints and cartilage. Thus, Crocin possesses a great anti-oxidant, anti-inflammatory, anti-atherosclerotic, anticonvulsant, anti-hypertensive, anti-nociceptive, anti-depressant, neuro-protective, and cytotoxic role [35,75,76].

4. Crocin anti-oxidant and anti-inflammatory effects on cancer

Natural products such as Crocin are gaining importance as potential therapeutic approach in treatment and prevention of cancer. Most of these compounds have been investigated in experimental studies and clinical trials with promising results [77–80]. Studies have shown that Crocin possesses potential anti-cancer properties in different types of cancers such as leukemia, breast, colorectal, pancreatic, prostate cancers and etc., and may serve as adjuvant chemotherapy agent [79–89]. Also, a study showed that Crocin protected rats against MTX-induced hepatotoxicity by improving antioxidant defense system and attenuating oxidative stress and inflammation, indicating that it can be used as a protective agent against chemotherapeutic toxicity [90].

The anti-tumor mechanism of Crocin include anti-proliferation, induction of cell cycle arrest and apoptosis, anti-oxidative and anti-inflammatory activities, stimulation of detoxification enzymes, and regulation of cancer related genes [84,91–94].

Crocin might suppress cell proliferation and cell cycle and induces apoptosis in cancer cells by up-regulation of Bax and p53, and activation of caspase-8, while down-regulation of Bcl-2, survivin and cyclin-D1 [95–98]. Also, Crocin down-regulates MRP1 and MRP2 and inhibits telomerase activity, and p21Cip1 overexpression [99,100].

Crocin treatment of adenocarcinoma cells leads to significant phenotypic changes including cell shrinkage, cytoplasmic vacuolization, and chromatin condensation (pyknotic nuclei). Moreover, Crocin might inhibit cancer cell proliferation by interacting with tubulin through depolymerization of microtubules [101]. In order to prevent cancer cell invasion and metastasis, Crocin down-regulates N-cadherin, β-catenin, metalloproteinases (MMP-2 and MMP-9) and urokinase-type plasminogen activator (uPA), up-regulates E-cadherin, and suppresses cell cycle at G1, G0/G1, S, and G2/M phases [102].

Tumor cells have rapid metabolism and mitochondrial dysfunction as well as increased levels of lipid oxidation and oncogene expression causing elevated levels of oxidative stress. Moreover, inflammation results in overproduction of ROS by over-activation of cytokine signaling, and pro-oxidant enzymes (NOX, LOX and COX) [103]. Likewise, over-activation of pro-oxidant enzymes increases inflammatory processes and results in malignancy. The high levels of oxidative stress aids cancer cells to gain uncontrolled proliferation, invasion, migration and angiogenesis through insensitivity to anti-proliferative and apoptosis signals, anchorage-independent cell growth, and epigenetic modification, however it is not sufficient to lead cancer cells towards apoptosis. Besides, malignant cells contain lower capacity of the enzymatic and non-enzymatic antioxidant defense system, and higher amount of metal ions (e.g., Cu^{2+} and Fe^{3+}), producing higher concentrations of ROS. In fact, antioxidants prevent tumor cell growth by modulating intracellular ROS generation and inhibiting uncontrolled cell proliferation. On the other hand, some chemotherapeutic drugs including cisplatin, and anti-cancer agents including Crocin, give rise to higher amount of ROS and increase excessive oxidative stress, leading to cytotoxicity and

cancer cell death [103–105]. Crocin acts as either an anti-oxidant or as a pro-oxidant and decreases antioxidant potential in cancer cells, thereby increasing their sensitivity to oxidative stress and leading to apoptosis [83].

Crocin could suppress growth of thyroid gland follicular carcinoma cells through ROS-dependent mitochondrial apoptosis by increasing ROS formation and mitochondrial membrane potential activity. Also, it up-regulated caspase-3, − 8 and − 9, Bax and lipid peroxidation, while down-regulated anti-oxidant enzymes (SOD, CAT, GSH), c-Myc, survivin, cyclin D1, and Bcl-2. Moreover, Crocin activates transcription signaling pathways and inhibits NF-κB, ERK and JAK/STAT signal transduction pathways [92,106].

Also, Crocin enhanced Nrf2 and HO-1 signaling and reduced caspase-3 activity, showing anti-ulcerogenic effects [107]. Nrf-2 regulates oxidative stress by up-regulation of antioxidant gene expressions and enzyme activity. Targeting Nrf-2 pathway is a therapeutic strategy in cancer treatment [108]. Crocin up-regulated Nrf-2 and HO-1 and suppressed KEAP-1 hepatic expression, regulating hepatic oxidative status and inhibiting hepatocellular carcinoma in rat [109]. Also, Crocin up-regulated Nrf-2 and anti-oxidant response elements (AREs) such as NQO1, NQO2, and HO-1 in HeLa cells [110].

Chronic and acute inflammation is associated with cancer occurrence, development, metastasis and recurrences of tumors and chemokines and inflammatory factors released by cancer cells play a crucial role in development of cancers [111]. Crocin reduces the mRNA expression of pro-inflammatory cytokines associated with cancer [112]. Also, Crocin suppressed proliferation of gastric adenocarcinoma cells by inhibiting TPM4 which is involved in cell proliferation. In addition, TPM protein regulates inflammatory myo-fibroblastic tumors through ALK receptors [91]. Moreover, Crocin has oncostatic effects on gastric cancer cells by inhibiting EMT, migration, and invasion through miR-320/KLF5/HIF-1α signaling [113].

Crocin shows anti-inflammatory properties by down-regulation of inflammatory markers including NF- κB [84,114]. Treatment with Crocin reduced the chemokines and inflammatory factors including MIP2, MCP 1, IL-8, IL-6, IL-1β and TNF-α through suppressing STAT3 signaling pathway in HCT116 cell line [111]. STAT3 signaling pathway mediates cancer cell proliferation, survival, angiogenesis, metastasis and drug resistance and hyperactivation of STAT3 results in tumor-induced immunosuppression [115]. Crocin synergistically increases 5-FU anti-proliferative and anti-invasive activities and exerts anti-oxidative and anti-inflammatory effects through suppressing PI3K/Akt and Wnt pathways and E-cadherin in colorectal cancer [116].

Following treatment with Crocin, cell cycle was arrested and p53, FAS/APO-1 and caspase-3 apoptosis-related proteins were up-regulated in ovarian cancer cells [117]. Crocin reduced interleukins and TNF-α in the sera and colon tissues of mouse model through NF-κB signaling [84]. NF-κB signaling regulates the levels of Bax and Bcl-2, and hyper-activation of NF-κB p65 and subsequent expression of pro-inflammatory cytokines are associated with ulcerative colitis and colorectal cancer. After activation of NF-κB, it mediates transcription of inflammatory factors and activates pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α [118,119]. Further, IL-6 activates IL-17, subsequently production of TNF-α and IL-1β, and elevating iNOS and COX-2. In a positive feedback, IL-1β triggers the production of IL-6 and activates Th17 cells and promotes inflammatory response and development of colorectal cancer. Crocin prevented ulcerative colitis and colorectal cancer in mice by decreasing the concentrations of phosphorylated IKK (α/β), IκBα and NF-κB p65 [84].

5. Crocin anti-oxidant and anti-inflammatory effects on cardiovascular system

Cardiovascular diseases (CVDs) are considered as a major third cause of death worldwide [120]. Nowadays, the growing evidence clarified the undeniable correlation between CVDs and initiating factors such as obesity, smoking, diet, excessive alcohol consumption, and stress. Under the light of studies, it is well known that the effect of one of these factors lonely or in combination, as well as hypertension, hypercholesterolemia, and atherosclerosis are paving the way for developing the different cardiac dysfunctions including infarction, arrhythmias, angina, or heart failure [121]. Exercise training are considering as a substantial and powerful therapeutic strategy for prevention of development and progression of CVDs, proposing as a problematic methods because as they are stressful through production of ROS are capable of setting the stage for damage to muscle tissue and other organs [122–124]. In this regards, some studies have addressed an axial role of ROS or free radicals in increasing the mortality rate of CVDs [125]. Although, the main cellular sources of ROS have not been fully understood, NADPH oxidase, endothelial xanthine oxidase, and neutrophil myeloperoxidase are appear to be the major and most important ones [126]. For centuries, plants have been using as a main tools for the treatment of various human diseases. Currently, the global interests are shifting to the identification of medicinal plants that possess pharmacological effects with little or no side effects, capable of applying as a remedy in different diseases especially CVDs [68]. Crocin, a hydrophilic carotenoid, is applying as a traditional medicine and has been reported to have various pharmacological activities, for example anti-cancer, anti-inflammatory, antioxidant, anti-atherosclerotic, and cardiovascular diseases protection effects [127]. Some studies have been reported that the protective roles of Crocin in CVDs are related to the modulation of endogenous antioxidant enzymatic activities and cardiac biomarkers [128,129]. Because of the well-known antioxidant and anti-inflammatory effects of Crocin [130], multiple human and animal studies have been scheduled to clarify the protection mechanisms of Crocin on cardiovascular disorder induced by oxidative stress and subsequently inflammation.

5.1. Cardiovascular dysfunction induced by diabetes and Crocin protection

Diabetes is one of the main reasons that make a contribution to cardiac dysfunction by impairing the calcium handling, mitochondrial dysfunction, oxidative stress, and inflammation. According to the studies, in vivo and in vitro, on the molecular cardio-protective mechanisms of Crocin in diabetes, it has been reported that Crocin treatment makes a contribution to increasing the phosphorylation of AMPK (5´ Adenosine Monophosphate-activated Protein Kinase), master regulator of cellular energy homeostasis, in cardiac muscles. Additionally, Feidantsis K et al. reported that Crocin has protection role in isolated cardiac myocytes exposed to a high concentration of glucose via affecting an autophagy and apoptosis pathways. It should be emphasized that these results are suggesting that Crocin is capable of improving the cardiac function in diabetic patients through inhibiting apoptosis and autophagy normalization in cardiac myocytes [131]. In another study by Dariushnejad H et al. on protective effect of Crocin on cardiomyopathy following Streptozotocin (STZ)-induced type 2 diabetes, they discovered that Crocin is able to augmenting the expression levels of miR-126 and mir-210, which occupy an axial role in neoangiogenesis, cell apoptosis inhibition, and rescue the cardiac system from lethal damage [132]. Ghorbanzadeh V et al. reported that in heart tissue treated by Crocin, multiple functions for instance promoting endothelial cell proliferation, migration, and micro-vascular leakage stimulation, contribute to increasing the protein expression level of VEGF-A (Vascular Endothelial Growth Factor A) and subsequently angiogenesis in diabetic animals [133].

5.2. Crocin modulate the cardiac ischemia/reperfusion injuries

One of the most common CVDs is cardiac ischemia-induced by coronary artery stenosis which is the consequence of myocardial blood flow limitation and low heart oxygen supply. According to the studies, it has been clarified that perfusion after acute myocardial ischemia occupies

an axial role in surviving, saving, and maintaining ischemic heart cell function, while reperfusion exerts a destructive effect on cells by triggering a sudden onset of oxidative reactions and local inflammatory response and finally makes a contribution to apoptosis and necrosis of cardiomyocytes during reperfusion [134,135]. ROS which are produced and increased during the cardiac reperfusion are considered as a one of the main elements in the pathophysiology of cardiac arrhythmias [136]. In this regard, the results of an animal and in vitro studies showed that Crocin in preventing the ischemia/reperfusion injuries is partially capable of suppressing ventricular arrhythmias and amplifying the antioxidant system in cardiac tissue respectively [137]. Esmaeilizadeh et al. reported that eNOS, an essential mediator of some endothelial growth stimulants including vascular endothelial growth factor and prostaglandin E2, performs as a mediator in vascular restructuring as well as a potent vasodilator. In this regard, to explain the NO-dependent cardiovascular protection against ischemia/ reperfusion injury and preserving the heart function, they pretreated post-ischemic isolated rat heart with Crocin. In this study they reported that as a result of Crocin pretreatment, nitric oxide synthase expression levels were increased in cardiac myocytes and endothelium [138]. Moreover, another study reported that Crocin improves autophagy during ischemia by modulating the activation of AMPK and protein kinase B (Akt) [139].

5.3. Cardiotoxicity and Crocin

Myocardial Infarction (MI), occurs due to a long-term imbalance between myocardial oxygen supplies and demand, is a complex phenomenon that affects the structural, electrical, mechanical, and biochemical properties of the circulatory system. Among the various risk factors the accumulation of free radicals has been characterized as a significant factor in the pathophysiology of acute MI. In the study on isoproterenol-induced cardiotoxicity, a beta-adrenoceptor, Goyal S et al. demonstrate that isoproterenol by creating an imbalance between oxidants and antioxidants in the myocardium is capable of paving the way for MI. In this study they revealed that Crocin through improving the cardiac antioxidant status, histo-pathological, and lipid profile indexes contributes to preventing the MI and the hemodynamic parameters maintenance. These results suggest Crocin as a preventive agent against MI [140]. DNZ, one of the most widely-used organophosphate toxins, contributes to cardiac toxicity by stimulating the ROS and oxidative stress production. In this context, the results are demonstrating that Crocin by decreasing lipid peroxidation and CK-MB level and increasing an antioxidant content that attenuates the Bax/Bcl2 ratio elevation and activation of caspase 3-induced by DNZ sub-chronic exposure makes a contribution to cardiac histo-pathological damages prevention [141]. In addition, it has been reported that Crocin by increasing and decreasing the ubiquitin Hypoxia-Inducible Factor 1 (HIF-1α) and protein ubiquitylation displays a protection role against DZN respectively [142].

Crocin as an alternative herbal therapy presents preventive and therapeutic effect with an anti-inflammatory and antioxidant mechanism of action that appears to treat various conditions related to cardiopulmonary reactions. Under the light of studies it has been disclosed that Crocin makes a contribution to apoptosis inhibition by increasing the Bax/Bcl2 expression level [143,144] and also Crocin exerts inhibitory effects on apoptosis by reducing the level of total serum cholesterol, TG, LDL-C and restricting the formation of aortic plaque [145]. Although, these desirable properties promise the future use of Crocin as a therapeutic agent in CVDs, it should be emphasis that more clinical trials and toxicological studies are needed in this regard [146].

6. Anti-neuro-inflammation and anti-oxidant action of Crocin

Crocin exerts its antioxidative, and anti-inflammatory roles in the treatment of a wide range of neurological disorders such as ADs and Parkinson's disease (PD) [44]. We will outline the important findings of scholars in the following paragraph.

A growing body of evidence indicates that Crocin alleviates oxidative stress and inflammation in ADs through targeting multiple ways like reduction of pro-inflammatory cytokines (IL-1 and TNF) [26,147–149], MDA levels [150,151], suppression of CX3CR1 up-regulation (inducer of microglial neuro-inflammation) [152], and increasing antioxidants (GPx and SOD) [153–158]. Similarly, Crocin has protective effects against PD via its anti-oxidative and anti-inflammatory properties [159]. In different animal models of neural damage, Crocin diminishes neural loss and ameliorates the symptoms of PD by increasing GSH [160–162], dopamine [160–162], and total thiols [161,162], and decreasing thiobarbituric acid reactive substance (TBARS) [160], NO [163], and AChE activity [161,162]. The anti-inflammatory and anti-oxidative roles of Crocin have been reported in other neurodegenerative disorders like ischemic brain injury [164–167], traumatic brain injury [168,169], spinal cord injury [170,171], and neuropathic pain [172], mostly through boosting anti-oxidants and reducing ROS. Ahmed et al. [44] thoroughly reviewed the therapeutic potentials of Crocin in the treatment of neurological disorders.

7. Crocin anti-oxidant and anti-inflammatory effects on diabetes

It has been demonstrated that in diabetes conditions, ROS are formed in a variety of tissues. The non-enzymatic glycosylation process the electrochemical reaction in mitochondria and membrane-bound NADPH oxidase are indeed sources of radicals in cells. ROS activated under diabetic situation which cause glucose toxicity in β- cells. β - Cells GLUT2 expression, resulting in very efficient uptake of glucose exposed in extreme glucose concentration [173,174]. Furthermore, due to vulnerability of β- cell to ROS, antioxidant enzymes such as CAT and GPx are expressed at a low level. It supposes that ROS by reduction of pancreatic and duodenal homeobox 1 (PDX-1) and/or MafA binding to the insulin gene trigger has a critical role in β- cells deterioration [175]. Moreover, chronic disposal of an extra concentration of glucose decrease the expression of insulin gene provides resistance to antioxidant treatment [176].

Insulin resistance and pancreatic β-cell disturbance are key features of type 2 diabetes [177]. Diabetic condition provide insulin resistance in a variety of insulin target tissues, including the liver, muscle, and fat. When insulin interacts to the insulin receptor on the cell surface, the insulin receptor and its substrates are phosphorylated, activating multiple insulin signaling pathways.

Type 1 diabetes (DT1) is a type of chronic inflammatory disease. In this metabolic disease, T-cells and monocytic cells permeate into pancreatic islets and cause hyperglycemia by insulin-producing β cells destroying. Hyperglycemia promotes ROS generation, resulting in an unbalance between the formation of ROS and antioxidant (defense system), which cause oxidative stress [178]. The free radicals cause an effect on β-cells via activating the transcription factor NF-κβ in macrophages [179,180].

Crocin reduced hyperlipidemia, indicating that it may help to avoid diabetes-related cardiovascular problems by lowering oxidative stress and dyslipidemia. In the animal model, Crocin could suppress pro-inflammatory cytokines such as TNF-α, IL-6 which indicated the therapeutic effect of Crocin in diabetes treatment [10]. Recent research indicates that NF-κβ oxidative activation stimulates LOX1 gene expression. In addition, LOX1 gene through promoting ROS generation induces cell damage. Moreover in clinical studies it has been demonstrated that there is a tight relationship between level of LOX1 and ROS production in human vascular smooth muscle cells and macrophages [181].

NF- κβ can activates protein-1 (AP1) which has a significant role in hepatocyte mortality in fatty liver and diabetic patients. Furthermore NF-κβ overexpression cause mitophagy increased and imperfection in mitochondrial biogenesis markers, sirtuin 1 (SIRT1), SIRT3, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1a), and long chain acetyl-COA coenzyme A dehydrogenase (LCAD) in hepatocytes. Crocin treatment dramatically decreased AP1 gene expression

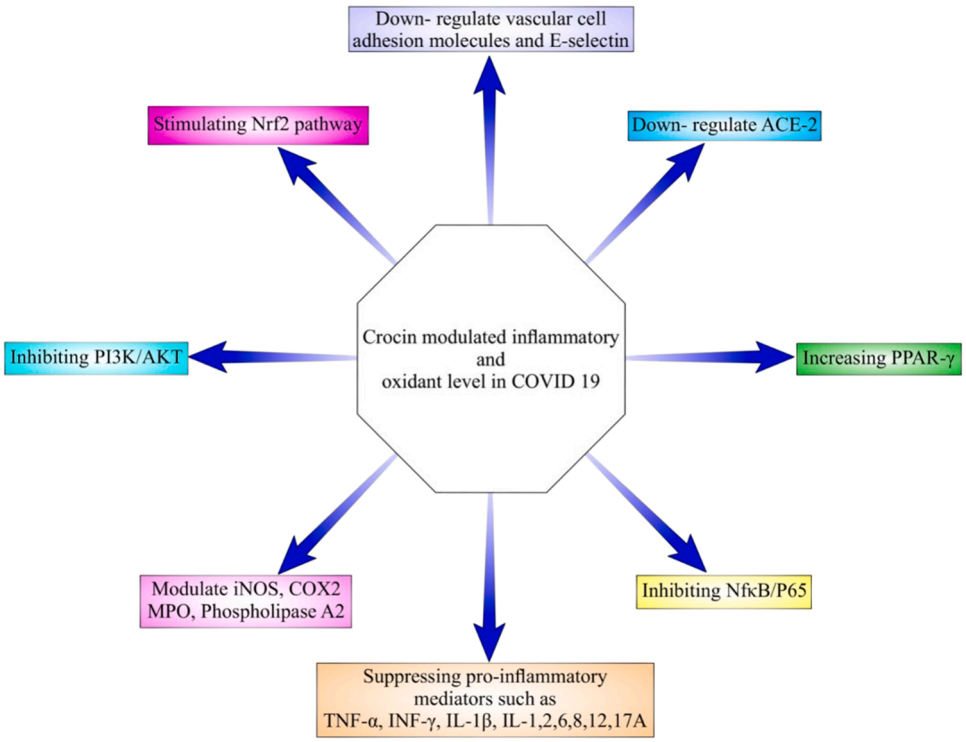

Fig. 2. Mechanisms of Crocin anti-inflammatory and anti-oxidant function in Covid19. The respiratory pandemic COVID-19 (Corona virus disease 2019), known as the most important pandemic of the 21st century, is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Nrf2; Nuclear factor-erythroid factor 2-related factor 2, ACE2; Angiotensin-converting enzyme 2, PPARɣ; Peroxisome proliferator- activated receptor gamma, MPO; Myeloperoxidase.

while increasing SIRT1 and LCAD gene expression in T2D rats' liver tissue [182]. Crocin, protects myocardium from diabetic problems by activating PPAR, enhancing antioxidant capacity, reducing inflammatory cytokines, and improving the activities of cardiac damage biomarkers. [183]. Crocin promotes AMP-activated protein kinase (AMPK) signaling, which has a positive effect on lipid and glucose metabolic dysfunction. AMPK activation reduces the CDK5 protein level, which is followed by a reduction in PPAR phosphorylation, inhibiting adipose growth and metabolic disorders [184].

Diabetes is related to cognitive deterioration and in this regard Crocin show a vital role in neuro-protective actions, the administration of Crocin in diabetic rats could have a protective effect on spatial learning and memory deficits. Although Crocin by modulation NO levels can improve the memory deficiency [185]. The Diabetic Nephropathy (DN) disease is one of the most common consequences of diabetes mellitus. Toll like receptors (TLRs) trigger pro-inflammatory signaling in the immune system, has been associated to diabetes mellitus metabolic disorders. TLR4 via hyperglycemia activates micro-albuminuria which caused renal TNF-α, NFκβ, and IL-6 signaling, potentially causing further nephrotoxicity [186]. Daily administration of Crocin (30 mg) effectively decrease concentrations of TNF-α, and NF-κβ in type 2 diabetes patients [187]. The conditions such as excessive ROS, hyperglycemia, oxidized low-density lipoprotein (LDL), can damage the endothelium and disrupt endothelial function which lead to a wide range of human disease, including diabetic vascular problems, chronic renal failure hypertension. It suggested the calcium-activated potassium channel (KCa3.1) in the mitochondrial inner membrane dysfunction associated with mitochondrial problems. Crocin through blockade ROS-generated by KCa3.1 can improves mitochondrial function in diabetes [62].

8. Crocin anti-oxidant and anti-inflammatory effects on stem cells

When it comes to research, especially in stem cells, paying attention to the factors, improving the differentiation of stem cells to interested cell lineage, is very important and noteworthy. The effects of Crocin on proliferation, migration, and differentiation of mesenchymal stem cells (MSCs) [188–190], human dental pulp stem cells [191], and neural stem cells [192] have been recently reported. In this regard, *nabiuni* research group in two papers [193,194] indicated that Crocin increases the differentiation of epidermal neural crests stem cells (EPI-NCSCs), a type of cells that has broadly been used for the treatment of many neurological disorders, into neural lineages; therefore, this therapeutic agent could improve differentiation potential of these stem cells in cell therapy of neurological disorders [193,194].

Yousefi et al. [190] published an interesting article regarding the anti-inflammatory and anti-oxidant effects of Crocin on MSCs. They demonstrated that Crocin increases the expression of anti-inflammatory cytokines and anti-oxidative factors at low doses and decreases inflammatory cytokines at higher doses [190].

9. Crocin anti-oxidant and anti-inflammatory effects on COVID19

The respiratory pandemic COVID-19 (Corona virus disease 2019), known as the most important pandemic of the 21st century, is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [195]. During the SARS-CoV-2 infection, immune cells are hyper-activated and results in overproduction of inflammatory cytokines such as TNFα, IL2, IL7, IL10, IP10, MIP1A, MCP1 and GCSF, leading to cytokine storm [196]. At the cellular level, SARS-CoV-2 may cause excessive production of ROS and redox imbalance, lipid peroxidation, activation of the permeability transition pores of the

mitochondria, cell death and detrimental inflammatory reaction, leading to failure in several organs such as lung, heart, brain and kidney [197–200].

From the molecular point of view, one of the main factors of cytokine storm during severe infections such as COVID-19 is the toll-like receptor 4 (TLR4)/toll/interleukin-1 receptor/resistance protein (TIR)-domain-containing adapter-inducing interferon-β (TRIF)/nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) pathway, thereby increasing cytokine production, vasculopathy, and coagulopathy. Moreover, SARS-CoV-2 induces the activation of JAK-STAT, C-reactive protein (CRP), and the colony-stimulating factor (CSF) [201–203].

Accumulating evidence has demonstrated the anti-SARS-CoV-2 potential of pharmaceutical active natural products (PANPs) using computational methods, wet lab and clinical trial studies [204–210]. Anti-SARS-CoV-2 natural products exert their therapeutic properties through different ways; some of them decrease the airway inflammation and edema, while others boost the immune system. Also, some natural products are being proposed as preventive treatment [211–216]. Additionally, anti-SARS-CoV-2 compounds might selectively block the viral life-cycle-related proteins and enzymes including ACE2 (angiotensin converting enzyme 2), TMPRSS2 (trans-membrane protease serine 2), PLPRO (papain-like proteinase) and 3CLpro (3-chymotrypsin like protease) [217,218].

In this regard, saffron has been used as a traditional herbal remedy to treatment of coughs, asthma, gastrointestinal disorders, amenorrhea, and cardiovascular and immune disorders [219]. Crocin exerts anti-SARS-CoV-2 effects (Fig. 2) in different ways including anti-inflammatory and anti-oxidative actions. Oxidative stress plays a central role in the pathogenesis of SARS-CoV-2 infection by over-production of inflammatory mediators and cell apoptosis [220]. A bunch of studies has shown that Crocin possesses anti-inflammatory effect in different organs by inhibiting PI3K/Akt, NF-κB, NF-κB p65, and nucleotide binding domain (NBD)-, leucine rich repeat (LRR)-, and pyrin domain (PYD)-containing protein 3 (NLRP3) inflammatory pathways [35,94]. In addition, Crocin modulates SARS-CoV-2-induced cytokine cascade and reduces pro-inflammatory enzymes including iNOS, COX-2, MPO, phospholipase A2, prostanoids [221,222]. Crocin reduced inflammation by suppressing pro-inflammatory mediators, such as TNF-α, IFN-γ, IL-1β, IL-1, IL-2, IL-6, IL-8, IL-12, and IL-17A, and NF-κB signaling pathway in Aspergillus fumigatus-treated human bronchial epithelial cells [223,224]. In a clinical trial conducted by 40 patients with multiple sclerosis, daily administration of Crocin for 4 weeks reduced TNF-α, IL-17, lipid peroxidation and DNA damage, and increased total antioxidant capacity [225].

SARS-CoV-2 enters into the host cells by binding its spike glycoproteins to angiotensin converting enzyme 2 (ACE2) receptors [226]. As ACE2 receptor is found in various organs such as lungs, heart, kidney, oral and nasal mucosa, stomach, intestine and bladder, cell-mediated immunity causes damage through cytokine storm and is considered as a main pathway of cell death in COVID-19 patients [227]. Crocin down-regulates angiotensin-converting enzyme 2 (ACE2) and cellular adhesion molecules including intercellular adhesion molecule, vascular cell adhesion molecule, and E-selectin [221,222].

An animal study showed that pretreatment of Crocin (50 mg/kg) inhibited the production of TNF-α and IL-1β, down-regulated iNOS, and reduced lung edema, thereby exerting a significant protective effect on mice with LPS-induced acute lung injury [228]. Similarly, cigarette smoke-induced chronic obstructive pulmonary disease (COPD) in mice model was improved by administration of Crocin through reducing inflammatory cells and pro-inflammatory cytokines and suppressing PI3K/ Akt mediated inflammatory pathways [229].

NF-κB and Nrf2 pathways are involved in SARS-CoV-2 infection, therefore Crocin has a protective role against CoV-induced lung injury by suppressing NF-κB and improving the capacity of the oxidative stress defense system by stimulation of Nrf2 pathway [230,231]. Besides, activation of Nrf2 following Crocin treatment leads to down-regulation of ACE2 receptors, thereby inhibiting viral entry to cells. Also, PPAR-γ inhibits over-production of cytokines and NF- κB pathway and Crocin has a potential immune-modulatory role by increasing the expression of PPAR-γ, preventing cytokine storm, and protecting against severe clinical symptoms of COVID-19 [222,224,232]. Also, bleomycin-induced pulmonary fibrosis in rat was improved after treatment with Crocin owing to its antioxidant, anti-inflammatory, and immuno-modulatory properties [233].

During SARS-CoV-2 infection, NF-κB and MAPK signaling pathways are activated, total number of CD4 + T cells, CD8 + T cells, IgE, IgM, and natural killer (NK) cells are decreased, and pro-inflammatory cytokines are increased. It has been proposed that carotenoids including Crocin might exert anti-viral properties by suppressing theses signaling pathways, increasing the total number of immune cells, and decreasing inflammatory cytokines [221]. Crocin could improve LPS-induced acute respiratory distress syndrome and vascular pulmonary edema in mice by suppressing MAPK and NF-κB inflammatory signaling pathways, down-regulation of MMP-9, heparinase, and cathepsin L, maintaining the integrity of glycocalyx, and increasing the pulmonary vascular permeability [234]. Regarding to study by Xiong et al., down-regulation of p-extracellular signal-regulated kinase, p-JNK, p-p38 and eotaxin, suppressing MAPK signaling pathways, and reducing interleukins of IL-4, IL-5, and IL-13 by Crocin results in improving airway inflammation and hyper-reactivity in a murine model, suggesting Crocin as a possible agent for treatment of patients with asthma [235]. In a similar study, Crocin showed significant anti-inflammatory and anti-oxidant effects against ovalbumin-induced allergic airway asthma in mice by modulating IL-4/IL- 13 signaling pathways, down-regulation of pro-inflammatory cytokines, and modulation of oxidant and antioxidant homeostasis [236].

Crocin might exert antiviral effects by preventing the viral replication. Studies show that Crocin has anti-HSV-1 and anti-HIV-1 potential and prevents virus entry and replication. According to the computational investigation using molecular docking, Crocin possesses a high binding affinity for the main protease of SARS-CoV-2 and acts as a potential inhibitor, suggesting its anti- SARS-CoV-2 properties [237]. Also, an in-silico study showed that Crocin-1 may exert antiviral effects by strong hydrogen bonding to the SARS-CoV-2 receptor binding domain/ACE2 complex [238]. It has been hypothesized that Crocin has anti-SARS-CoV-2 effects by protecting cardiovascular and cerebrovascular damage owing to thromboembolic events after SARS-CoV-2 infection and keeping the lung and cardiovascular systems safe [203,224].

10. Crocin anti-oxidant and anti-inflammatory effects on renal system

Renal toxicity which is known as nephrotoxicity can be an effect of hemodynamic variation, cell and inflammatory tissue damage and/or occlusion of renal excretion. The numerous condition such as therapeutic drugs and environmental pollutants can induce nephrotoxicity [239]. In this regard the main side effect of chemotherapy is nephrotoxicity. A large accumulation of chemo-drug like cisplatin in kidney is the main pathway for drug excretion. Recent studies have indicated that lipid peroxidation, ROS production via the mitochondria, and the xanthine oxidase system in tubular cells play roles in the pathophysiology of cisplatin renal injury [240]. In addition, OS causes apoptosis by increasing ROS, lipid hydroperoxides (LOOH), and MDA, in addition to decreasing SOD, GSH-Px, CAT, GSH [241]. The various studies have revealed that ROS are strongly associated to cisplatin-induced acute nephrotoxicity. The recent investigations found that Crocin significantly reduced cisplatin-induced renal failure in rats [242]. Moreover, MTX can cause OS and renal glomeruli damage, and according to the findings of a studies it seems Crocin could protect male rats' kidneys against the progressive consequences of MTX nephrotoxicity [66]. The concentration of NO in MTX groups was significantly higher than in the control group. Crocin administration the levels of NO were significantly

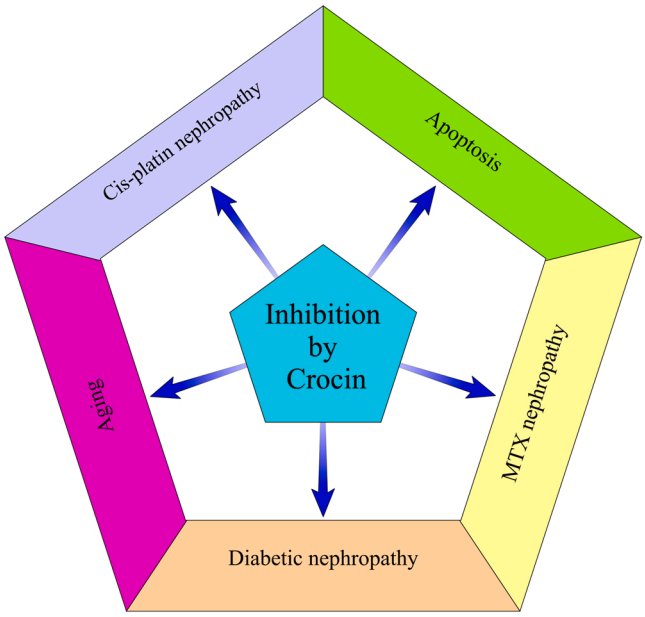

Fig. 3. The inhibitory role of Crocin in nephropathy. Crocin significantly reduced cisplatin-induced renal failure, Diabetic & MTX nephropaty, Apotosis and aging. MTX; Methotrexate.

decreased. NO is suspected to promote cell death through activating the P53 pathway and cGMP, as well as modulating the expressions of BCL2 and Bcl-xl. In pathologic states, iNOS creates NO molecules, which can lead to DNA damage and the breakdown of various lipid and protein molecules. Crocin prevents lipid peroxidation, which helps to keep cell membranes stable [243].

Decrease in physiological function of kidney, can be observed with aging. In comparison to another organ, the kidney function shows the most damage as individuals get older. Various factors such as oxidative stress and the molecular inflammatory pathways are effective in kidney aging. In this regard inactivating the signaling of inflammatory genes such as TNF-α, interleukin-6 (IL-6) could be a key target for treating the inflammatory response in the kidneys of elderly rats. Crocin therapy decrease adverse results in the aged rats and enhanced overall renal function in aged rats, including serum urea nitrogen [244].

Diabetic nephropathy (DN) and destruction of the glomerular filtration barrier is an important challenge in diabetes. Hyperglycemia and evaluated high levels of glucose concentration in diabetic patients have been associated with an increase in TLR4 mRNA and protein expression in human monocytes through NF-κβ activation [245]. Treatment of diabetic nephropathy includes interference with a variety of steps, including control of glucose levels, raising insulin levels, inhibit the oxidative stress and even interference with several immunological inflammatory mediators associated with DN pathogenesis. Attractively, Crocin has been shown to reduce blood glucose levels and insulin resistance, as well as to prevent obesity and improve lipid profiles (Fig. 3).

11. Conclusion

The use of herbs as the main drug or adjunctive therapy has been considered by researchers in recent decades. Numerous studies show the positive effect of Crocin to reduce inflammation and OS in many diseases condition such as cancer, renal disease, Covid19, diabetes and so on. On the other hand, use of stem cells is very interesting method in the treatment of diseases and one of the challenges in this field is to keep these cells in stem conditions, that Crocin can be help to overcome these challenges. On the other hand, Crocin can be effective in the treatment of covid19 disease, which has become one of the serious health challenges recently.

Table 1
Anti-cancer effect of Crocin.

Effect	Mechanism
Cell proliferation, cell cycle suppression and induces apoptosis	• Up-regulation of Bax and p53, • Activation of caspase-8, • Down-regulation of Bcl-2, survivin and cyclin-D1. • Down-regulation MRP1 and MRP2 • Inhibition telomerase activity, • Inhibition of p21Cip1 overexpression • Interacting with tubulin through depolymerization of microtubules • Suppresses cell cycle at G1, G0/G1, S, and G2/M phases • Increase excessive oxidative stress • ROS-dependent mitochondrial apoptosis • Up-regulation caspase-3, − 8 and − 9, Bax and lipid peroxidation • inhibiting TPM4
Prevent cancer cell invasion and metastasis	• Down-regulates N-cadherin, β-catenin, metalloproteinases (MMP-2 and MMP-9) and urokinase-type plasminogen activator (uPA) • Upregulates E-cadherin • Inhibits NF-κB, ERK and JAK/STAT signal transduction pathways • Inhibiting EMT • Inhibiting miR-320/KLF5/HIF-1α signaling pathway
Modulate oxadant effects and inflammatory condition	• Enhanced Nrf2 and HO-1 signaling • Down-regulated anti-oxidant enzymes (SOD, CAT, GSH) • Suppressed KEAP-1 • Up-regulated Nrf-2 and anti-oxidant response elements (AREs) such as NQO1, NQO2 • Reduces the mRNA expression of pro-inflammatory cytokines • Reduced the chemokines and inflammatory factors including MIP2, MCP 1, IL-8, IL-6, IL-1β and TNF-α through suppressing STAT3 signaling pathway • Decreasing the concentrations of phosphorylated IKK (α/β), IκBα and NF-κB p65
Synergic effect with chemotherapy drugs	• Increases 5-FU anti-proliferative and anti-invasive activities and exerts anti-oxidative and anti-inflammatory effects through suppressing PI3K/Akt and Wnt pathways and E-cadherin

It is hypothesized that saffron and its bioactive component, Crocin, may have the potential to limit the progression and severity of the SARS-CoV2 infection via its anti-oxidative, anti-inflammatory, immune-modulatory, and pulmono-protective effects. Therefore, Crocin can be considered as an adjunctive therapy in existing treatments for cardio-vascular-renal disease and cancer.(Table 1).

Conflict of interest statement

All authors declare that there is no conflict of interest.

Data availability

No data was used for the research described in the article.

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References

[1] J. Shiralizadeh, H. Barmaki, S. Haiaty, Y. Faridvand, M. Mostafazadeh, N. Mokarizadeh, et al., The effects of high and low doses of folic acid on oxidation of protein levels during pregnancy: a randomized double-blind clinical trial, Horm. Mol. Biol. Clin. Investig. 33 (3) (2018).

[2] N. Seyfizadeh, M. Tazehkand, A. Palideh, N. Maroufi, D. Hassanzadeh, M. Rahmati-Yamchi, et al., Is arbutin an effective antioxidant for the discount of oxidative and nitrosative stress in Hep-G2 cells exposed to tert-butyl hydroperoxide? Bratisl. Lek. Listy 120 (8) (2019) 569–575.

[3] P. Poprac, K. Jomova, M. Simunkova, V. Kollar, C.J. Rhodes, M. Valko, Targeting free radicals in oxidative stress-related human diseases, Trends Pharmacol. Sci. 38 (7) (2017) 592–607.

[4] R.D. Klein, V.D. Borges, C.E. Rosa, E.P. Colares, R.B. Robaldo, P.E. Martinez, et al., Effects of increasing temperature on antioxidant defense system and oxidative stress parameters in the Antarctic fish Notothenia coriiceps and Notothenia rossii, J. Therm. Biol. 68 (2017) 110–118.

[5] S. Furukawa, T. Fujita, M. Shimabukuro, M. Iwaki, Y. Yamada, Y. Nakajima, et al., Increased oxidative stress in obesity and its impact on metabolic syndrome, J. Clin. Investig. 114 (12) (2017) 1752–1761.

[6] C.R. Bosoi, C.F. Rose, Oxidative stress: a systemic factor implicated in the pathogenesis of hepatic encephalopathy, Metab. brain Dis. 28 (2) (2013) 175–178.

[7] H. Yaribeygi, M.T. Mohammadi, A. Sahebkar, Crocin potentiates antioxidant defense system and improves oxidative damage in liver tissue in diabetic rats, Biomed. Pharmacother. 98 (2018) 333–337.

[8] L. Chen, H. Deng, H. Cui, J. Fang, Z. Zuo, J. Deng, et al., Inflammatory responses and inflammation-associated diseases in organs, Oncotarget 9 (6) (2018) 7204.

[9] S. Missiroli, I. Genovese, M. Perrone, B. Vezzani, V.A. Vitto, C. Giorgi, The role of mitochondria in inflammation: from cancer to neurodegenerative disorders, J. Clin. Med. 9 (3) (2020) 740.

[10] S. Korani, M. Korani, T. Sathyapalan, A. Sahebkar, Therapeutic effects of Crocin in autoimmune diseases: a review, BioFactors (Oxf., Engl.) 45 (6) (2019) 835–843.

[11] V. Vahedian, A. Asadi, P. Esmaeili, S. Zamani, R. Zamani, S. Hajazimian, et al., Anti-inflammatory activity of emu oil-based nanofibrous scaffold through downregulation of IL-1, IL-6, and TNF-α pro-inflammatory cytokines, Horm. Mol. Biol. Clin. Investig. 41 (2) (2020).

[12] N. Mokarizadeh, P. Karimi, M. Erfani, S. Sadigh-Eteghad, N.F. Maroufi, N. Rashtchizadeh, β-Lapachone attenuates cognitive impairment and neuroinflammation in beta-amyloid induced mouse model of Alzheimer's disease, Int. Immunopharmacol. 81 (2020), 106300.

[13] A. Tupal, M. Sabzichi, R. Bazzaz, N. Fathi Maroufi, M. Mohammadi, S. M. Pirouzpanah, et al., Application of α-tocotrienol-loaded biocompatible precirol in attenuation of doxorubicin dose-dependent behavior in HUH-7 hepatocarcinoma cell line, Nutr. Cancer 72 (4) (2020) 653–661.

[14] S. Haiaty, M.R. Rashidi, M. Akbarzadeh, N.F. Maroufi, B. Yousefi, M. Nouri, Targeting vasculogenic mimicry by phytochemicals: a potential opportunity for cancer therapy, IUBMB life 72 (5) (2020) 825–841.

[15] N. Juaid, A. Amin, A. Abdalla, K. Reese, Z. Alamri, M. Moulay, et al., Anti-hepatocellular carcinoma biomolecules: molecular targets insights, Int. J. Mol. Sci. 22 (19) (2021) 10774.

[16] A.A. Hamza, G.H. Heeba, S. Hamza, A. Abdalla, A. Amin, Standardized extract of ginger ameliorates liver cancer by reducing proliferation and inducing apoptosis through inhibition oxidative stress/inflammation pathway, Biomed. Pharmacother. 134 (2021), 111102.

[17] C. Mu, Y. Sheng, Q. Wang, A. Amin, X. Li, Y. Xie, Potential compound from herbal food of Rhizoma Polygonati for treatment of COVID-19 analyzed by network pharmacology: Viral and cancer signaling mechanisms, J. Funct. Foods 77 (2021), 104149.

[18] J. Bhat, R. Broker, Riboflavine and thiamine contents of saffron, Crocus sativus linn, Nature 172 (4377) (1953) 544.

[19] B. Javadi, A. Sahebkar, S.A. Emami, A survey on saffron in major Islamic traditional medicine books, Iran. J. Basic Med. Sci. 16 (1) (2013) 1.

[20] S.A. Moallem, A.T. Hariri, M. Mahmoudi, H. Hosseinzadeh, Effect of aqueous extract of Crocus sativus L.(saffron) stigma against subacute effect of diazinon on specific biomarkers in rats, Toxicol. Ind. Health 30 (2) (2014) 141–146.

[21] A. Gismondi, M. Serio, L. Canuti, A. Canini, Biochemical, antioxidant and antineoplastic properties of Italian saffron (Crocus sativus L.), Am. J. Plant Sci. 3 (11) (2012) 1573.

[22] R. Srivastava, H. Ahmed, R. Dixit, Crocus sativus L.: a comprehensive review, Pharmacogn. Rev. 4 (8) (2010) 200.

[23] G.L. Alonso, M.R. Salinas, J. Garijo, M.A. Sánchez-Fernández, Composition of crocins and picrocrocin from Spanish saffron (Crocus sativus L.), J. Food Qual. 24 (3) (2001) 219–233.

[24] R. Hoshyar, H. Mollaei, A comprehensive review on anticancer mechanisms of the main carotenoid of saffron, crocin, J. Pharm. Pharmacol. 69 (11) (2017) 1419–1427.

[25] H. Yaribeygi, M.T. Mohammadi, R. Rezaee, A. Sahebkar, Crocin improves renal function by declining Nox-4, IL-18, and p53 expression levels in an experimental model of diabetic nephropathy, J. Cell. Biochem. 119 (7) (2018) 6080–6093.

[26] K.N. Nam, Y.-M. Park, H.-J. Jung, J.Y. Lee, B.D. Min, S.-U. Park, et al., Anti-inflammatory effects of crocin and crocetin in rat brain microglial cells, Eur. J. Pharmacol. 648 (1–3) (2010) 110–116.

[27] I.N. Jam, A.H. Sahebkar, S. Eslami, N. Mokhber, M. Nosrati, M. Khademi, et al., The effects of crocin on the symptoms of depression in subjects with metabolic syndrome, Adv. Clin. Exp. Med. 26 (6) (2017) 925–930.

[28] L. Xi, Z. Qian, P. Du, J. Fu, Pharmacokinetic properties of crocin (crocetin digentiobiose ester) following oral administration in rats, Phytomedicine 14 (9) (2007) 633–636.

[29] I. Nikbakht-Jam, M. Khademi, M. Nosrati, S. Eslami, M. Foroutan-Tanha, A. Sahebkar, et al., Effect of crocin extracted from saffron on pro-oxidant–anti-oxidant balance in subjects with metabolic syndrome: a randomized, placebo-controlled clinical trial, Eur. J. Integr. Med. 8 (3) (2016) 307–312.

[30] M. Ebadi, Pharmacodynamic basis of herbal medicine, CRC press, 2006.

[31] F. Abdullaev, J. Espinosa-Aguirre, Biomedical properties of saffron and its potential use in cancer therapy and chemoprevention trials, Cancer Detect. Prev. 28 (6) (2004) 426–432.

[32] Y.-Q. Zheng, J.-X. Liu, J.-N. Wang, L. Xu, Effects of crocin on reperfusion-induced oxidative/nitrative injury to cerebral microvessels after global cerebral ischemia, Brain Res. 1138 (2007) 86–94.

[33] A. Poma, G. Fontecchio, G. Carlucci, G. Chichiricco, Anti-inflammatory properties of drugs from saffron crocus, Anti-Inflamm. Anti-Allergy Agents Med. Chem. (Former. Curr. Med. Chem. -Anti-Inflamm. Anti-Allergy Agents) 11 (1) (2012) 37–51.

[34] R. El-Kharrag, A. Amin, S. Hisaindee, Y. Greish, S.M. Karam, Development of a therapeutic model of precancerous liver using crocin-coated magnetite nanoparticles, Int. J. Oncol. 50 (1) (2017) 212–222.

[35] M. Hashemzaei, C. Mamoulakis, K. Tsarouhas, G. Georgiadis, G. Lazopoulos, A. Tsatsakis, et al., Crocin: a fighter against inflammation and pain, Food Chem. Toxicol. (2020), 111521.

[36] R.A. Dar, P.K. Brahman, N. Khurana, J.A. Wagay, Z.A. Lone, M.A. Ganaie, et al., Evaluation of antioxidant activity of crocin, podophyllotoxin and kaempferol by chemical, biochemical and electrochemical assays, Arab. J. Chem. 10 (2017) S1119–S1128.

[37] B.S. Yousefsani, S. Mehri, J. Pourahmad, H. Hosseinzadeh, Crocin prevents sub-cellular organelle damage, proteolysis and apoptosis in rat hepatocytes: a justification for its hepatoprotection, Iran. J. Pharm. Res.: IJPR 17 (2) (2018) 553.

[38] F. Bouvier, C. Suire, J. Mutterer, B. Camara, Oxidative remodeling of chromoplast carotenoids: identification of the carotenoid dioxygenase CsCCD and CsZCD genes involved in Crocus secondary metabolite biogenesis, Plant Cell 15 (1) (2003) 47–62.

[39] M.K. Dhar, M. Sharma, A. Bhat, N.K. Chrungoo, S. Kaul, Functional genomics of apocarotenoids in saffron: insights from chemistry, molecular biology and therapeutic applications, Brief. Funct. Genom. 16 (6) (2017) 336–347.

[40] Y. Zhang, F. Fei, L. Zhen, X. Zhu, J. Wang, S. Li, et al., Sensitive analysis and simultaneous assessment of pharmacokinetic properties of crocin and crocetin after oral administration in rats, J. Chromatogr. B. 1044 (2017) 1–7.

[41] A. Asai, T. Nakano, M. Takahashi, A. Nagao, Orally administered crocetin and crocins are absorbed into blood plasma as crocetin and its glucuronide conjugates in mice, J. Agric. Food Chem. 53 (18) (2005) 7302–7306.

[42] A.H. Mohammadpour, M. Ramezani, N.T. Anaraki, B. Malaekeh-Nikouei, S. A. Farzad, H. Hosseinzadeh, Development and validation of HPLC method for determination of crocetin, a constituent of saffron, in human serum samples, Iran. J. Basic Med. Sci. 16 (1) (2013) 47.

[43] Y. Zhang, J. Geng, Y. Hong, L. Jiao, S. Li, R. Sun, et al., Orally administered crocin protects against cerebral ischemia/reperfusion injury through the metabolic transformation of crocetin by gut microbiota, Front. Pharmacol. 10 (2019) 440.

[44] S. Ahmed, M.M. Hasan, M. Heydari, A. Rauf, S. Bawazeer, T. Abu-Izneid, et al., Therapeutic potentials of crocin in medication of neurological disorders, Food Chem. Toxicol. 145 (2020), 111739.

[45] A.H. Mohamadpour, Z. Ayati, M.R. Parizadeh, O. Rajbai, H. Hosseinzadeh, Safety evaluation of crocin (a constituent of saffron) tablets in healthy volunteers, Iran. J. Basic Med. Sci. 16 (1) (2013) 39.

[46] A. Talaei, M.H. Moghadam, S.A.S. Tabassi, S.A. Mohajeri, Crocin, the main active saffron constituent, as an adjunctive treatment in major depressive disorder: a randomized, double-blind, placebo-controlled, pilot clinical trial, J. Affect. Disord. 174 (2015) 51–56.

[47] T. Senoner, W. Dichtl, Oxidative stress in cardiovascular diseases: still a therapeutic target? Nutrients 11 (9) (2019) 2090.

[48] D.S. Simpson, P.L. Oliver, ROS generation in microglia: understanding oxidative stress and inflammation in neurodegenerative disease, Antioxidants 9 (8) (2020) 743.

[49] M. Bobadilla, J. García-Sanmartín, A. Martínez, Natural food supplements reduce oxidative stress in primary neurons and in the mouse brain, Suggesting applications in the prevention of neurodegenerative diseases, Antioxidants 10 (1) (2021) 46.

[50] C. Hu, X. Zhang, N. Zhang, W.Y. Wei, L.L. Li, Z.G. Ma, et al., Osteocrin attenuates inflammation, oxidative stress, apoptosis, and cardiac dysfunction in doxorubicin-induced cardiotoxicity, Clin. Transl. Med. 10 (3) (2020), e124.

[51] H. Shokr, I.H. Dias, D. Gherghel, Microvascular function and oxidative stress in adult individuals with early onset of cardiovascular disease, Sci. Rep. 10 (1) (2020) 1–8.

[52] E. Khashchenko, M. Vysokikh, E. Uvarova, L. Krechetova, V. Vtorushina, T. Ivanets, et al., Activation of systemic inflammation and oxidative stress in adolescent girls with polycystic ovary syndrome in combination with metabolic disorders and excessive body weight, J. Clin. Med. 9 (5) (2020) 1399.

[53] R. Tian, R. Peng, Z. Yang, Y.-Y. Peng, N. Lu, Supplementation of dietary nitrate attenuated oxidative stress and endothelial dysfunction in diabetic vasculature through inhibition of NADPH oxidase, Nitric Oxide 96 (2020) 54–63.

[54] K. Neha, M.R. Haider, A. Pathak, M.S. Yar, Medicinal prospects of antioxidants: a review, Eur. J. Med. Chem. 178 (2019) 687–704.
[55] A. Chahal, A.K. Saini, A.K. Chhillar, R.V. Saini, Natural antioxidants as defense system against cancer, Asian J. Pharm. Clin. Res. (2018) 38–44.
[56] H.S. Hamed, S.M. Ismal, C. Faggio, Effect of allicin on antioxidant defense system, and immune response after carbofuran exposure in Nile tilapia, Oreochromis niloticus, Comp. Biochem. Physiol. Part C: Toxicol. Pharmacol. 240 (2021), 108919.
[57] N. Rahiman, M. Akaberi, A. Sahebkar, S.A. Emami, Z. Tayarani-Najaran, Protective effects of saffron and its active components against oxidative stress and apoptosis in endothelial cells, Microvasc. Res. 118 (2018) 82–89.
[58] H. Yaribeygi, A. Noroozadeh, M.T. Mohammadi, T.P. Johnston, A. Sahebkar, Crocin improves oxidative stress by potentiating intrinsic anti-oxidant defense systems in pancreatic cells during uncontrolled hyperglycemia, J. Pharmacopunct. 22 (2) (2019) 83.
[59] S.A. Abdulkareem Aljumaily, M. Demir, H. Elbe, G. Yigitturk, Y. Bicer, E. Altinoz, Antioxidant, anti-inflammatory, and anti-apoptotic effects of crocin against doxorubicin-induced myocardial toxicity in rats, Environ. Sci. Pollut. Res. (2021) 1–12.
[60] T. Ochiai, S. Soeda, S. Ohno, H. Tanaka, Y. Shoyama, H. Shimeno, Crocin prevents the death of PC-12 cells through sphingomyelinase-ceramide signaling by increasing glutathione synthesis, Neurochem. Int. 44 (5) (2004) 321–330.
[61] A. Kapucu, Crocin ameliorates oxidative stress and suppresses renal damage in streptozotocin induced diabetic male rats, Biotech. Histochem. 96 (2) (2021) 153–160.
[62] X. Li, Y. Liu, A. Cao, C. Li, L. Wang, Q. Wu, et al., Crocin improves endothelial mitochondrial dysfunction via GPx1/ROS/KCa3.1 signal axis in diabetes, Front. Cell Dev. Biol. 9 (2021), 651434.
[63] R. Kakkar, S.V. Mantha, J. Radhi, K. Prasad, J. Kalra, Increased oxidative stress in rat liver and pancreas during progression of streptozotocin-induced diabetes, Clin. Sci. 94 (6) (1998) 623–632.
[64] M.A. Hussain, N.M. Abogresha, G. AbdelKader, R. Hassan, E.Z. Abdelaziz, S. M. Greish, Antioxidant and anti-inflammatory effects of crocin ameliorate doxorubicin-induced nephrotoxicity in rats, Oxid. Med. Cell. Longev. 2021 (2021).
[65] M. Mehrabani, M. Goudarzi, S. Mehrzadi, A. Siahpoosh, M. Mohammadi, H. Khalili, et al., Crocin: a protective natural antioxidant against pulmonary fibrosis induced by bleomycin, Pharmacol. Rep. 72 (4) (2020) 992–1001.
[66] C. Jalili, A. Ghanbari, S. Roshankhah, M.R. Salahshoor, Toxic effects of methotrexate on rat kidney recovered by crocin as a consequence of antioxidant activity and lipid peroxidation prevention, Iran. Biomed. J. 24 (1) (2020) 39.
[67] V. Longobardi, G. della Valle, F. Iannaccone, A. Calabria, G. Di Vuolo, S. Damiano, et al., Effects of the antioxidant crocin on frozen-thawed buffalo (Bubalus bubalis) sperm, Ital. J. Anim. Sci. 20 (1) (2021) 2095–2101.
[68] K. Zeka, P. Marrazzo, M. Micucci, K.C. Ruparelia, R.R. Arroo, G. Macchiarelli, et al., Activity of antioxidants from crocus sativus l. petals: potential preventive effects towards cardiovascular system, Antioxidants 9 (11) (2020) 1102.
[69] R. Nassar, S. Eid, R. Chahine, B. Chabi, A. Bonnieu, M. El Sabban, et al., Antioxidant effects of lebanese Crocus sativus L. and its main components, crocin and safranal, on human skeletal muscle cells, Eur. J. Integr. Med. 40 (2020), 101250.
[70] M. Dianat, M. Radan, S.A. Mard, F. Sohrabi, S.S.N. Saryazdi, Contribution of reactive oxygen species via the OXR1 signaling pathway in the pathogenesis of monocrotaline-induced pulmonary arterial hypertension: the protective role of Crocin, Life Sci. 256 (2020), 117848.
[71] Y. Liang, B. Zheng, J. Li, J. Shi, L. Chu, X. Han, et al., Crocin ameliorates arsenic trioxide-induced cardiotoxicity via Keap1-Nrf2/HO-1 pathway: Reducing oxidative stress, inflammation, and apoptosis, Biomed. Pharmacother. 131 (2020), 110713.
[72] J.D. Hayes, A.T. Dinkova-Kostova, K.D. Tew, Oxidative stress in cancer, Cancer Cell (2020).
[73] H. Najafi, Z.M. Yarijani, M. Najafi, Theoretical and experimental in vivo study of antioxidant activity of crocin in order to propose novel derivatives with higher antioxidant activity and their delivery via nanotubes and nanocones, Inflammation 40 (5) (2017) 1794–1802.
[74] T. Ochiai, S. Ohno, S. Soeda, H. Tanaka, Y. Shoyama, H. Shimeno, Crocin prevents the death of rat pheochromyctoma (PC-12) cells by its antioxidant effects stronger than those of α-tocopherol, Neurosci. Lett. 362 (1) (2004) 61–64.
[75] B. Mesbahzadeh, M. Hassanzadeh-Taheri, M.-s Aliparast, P. Baniasadi, M. Hosseini, The protective effect of crocin on cisplatin-induced testicular impairment in rats, Bmc Urol. 21 (1) (2021) 1–9.
[76] S. Mirzaee, M.E. Bayatpoor, S. Shahyad, M.T. Mohammadi, Z. Bahari, The protective effects of Crocin on testopathy in fat-fed and streptozotocin-treated diabetic rats: An experimental study, Int. J. Reprod. Biomed. 17 (2) (2019) 89.
[77] M.B. Yerer, Natural Products in Clinical Trials, 40, Multidisciplinary Digital Publishing Institute Proceedings,, 2019, p. 32.
[78] A. Amin A., A. Hamza, S. Daoud, K. Khazanehdari, A. Al Hrout, B. Baig, et al., Saffron-based crocin prevents early lesions of liver cancer: in vivo, in vitro and network analyses, Recent Pat. anti-Cancer Drug Discov. 11 (1) (2016) 121–133.
[79] H.A. Bakshi, M.S. Al Zoubi, H.L. Faruck, A.A. Aljabali, F.A. Rabi, A.A. Hafiz, et al., Dietary crocin is protective in pancreatic cancer while reducing radiation-induced hepatic oxidative damage, Nutrients 12 (6) (2020) 1901.
[80] A. Farahi, M.R. Abedini, H. Javdani, L. Arzi, E. Chamani, R. Farhoudi, 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) 1–11.
[81] A.S. Jahromi, M. Kargar, F. Kafilzadeh, M. Jamalidoust, M. Moradzadeh, Crocin promotes apoptosis in human EBV-transformed B-lymphocyte via intrinsic pathway, Mediterr. J. Hematol. Infect. Dis. 13 (1) (2021).
[82] K. Zhang, L. Wang, S. Si, Y. Sun, W. Pei, Y. Ming, et al., Crocin improves the proliferation and cytotoxic function of T cells in children with acute lymphoblastic leukemia, Biomed. Pharmacother. 99 (2018) 96–100.
[83] A. Nasimian, P. Farzaneh, F. Tamanoi, S.Z. Bathaie, Cytosolic and mitochondrial ROS production resulted in apoptosis induction in breast cancer cells treated with Crocin: The role of FOXO3a, PTEN and AKT signaling, Biochem. Pharmacol. 177 (2020), 113999.
[84] S. Teng, J. Hao, H. Bi, C. Li, Y. Zhang, Y. Zhang, et al., The protection of crocin against ulcerative colitis and colorectal cancer via suppression of NF-κB-mediated inflammation, Front. Pharmacol. 12 (2021) 377.
[85] Qar J., Al-Trad B., Al Zoubi MS, Fayyad D., Aljabali AA, Omari S., et al. Crocintreatment improves testosterone induced benign prostatic hyperplasia in rats. 2021.
[86] R. Salek, M. Dehghani, S.A. Mohajeri, A. Talaei, A. Fanipakdel, S.A. Javadinia, Amelioration of anxiety, depression, and chemotherapy related toxicity after crocin administration during chemotherapy of breast cancer: a double blind, randomized clinical trial, Phytother. Res. 35 (9) (2021) 5143–5153.
[87] F. Vali, V. Changizi, M. Safa, Synergistic apoptotic effect of crocin and paclitaxel or crocin and radiation on MCF-7 cells, a type of breast cancer cell line, Int. J. Breast Cancer 2015 (2015).
[88] S. Chen, S. Zhao, X. Wang, L. Zhang, E. Jiang, Y. Gu, et al., Crocin inhibits cell proliferation and enhances cisplatin and pemetrexed chemosensitivity in lung cancer cells, Transl. lung Cancer Res. 4 (6) (2015) 775.
[89] Y. Luo, S. Cui, F. Tang, C. Shen, Y. Qi, D. Lu, et al., The combination of crocin with cisplatin suppresses growth of gastric carcinoma cell line BGC-823 and promotes cell apoptosis, Pak. J. Pharm. Sci. 30 (2017) 5.
[90] M. Kalantar, H. Kalantari, M. Goudarzi, L. Khorsandi, S. Bakhit, H. Kalantar, Crocin ameliorates methotrexate-induced liver injury via inhibition of oxidative stress and inflammation in rats, Pharmacol. Rep. 71 (4) (2019) 746–752.
[91] Y. Luo, P. Yu, J. Zhao, Q. Guo, B. Fan, Y. Diao, et al., Inhibitory effect of crocin against gastric carcinoma via regulating TPM4 gene, OncoTargets Ther. 14 (2021) 111.
[92] Y. Zhang, M. Zhu, S. Krishna Mohan, Z. Hao, Crocin treatment promotes the oxidative stress and apoptosis in human thyroid cancer cells FTC-133 through the inhibition of STAT/JAK signaling pathway, J. Biochem. Mol. Toxicol. 35 (1) (2021), e22608.
[93] X. Chen, J. Huang, Y. Lv, Y. Chen, J. Rao, Crocin exhibits an antihypertensive effect in a rat model of gestational hypertension and activates the Nrf-2/HO-1 signaling pathway, Hypertens. Res. 44 (6) (2021) 642–650.
[94] X. Bi, Z. Jiang, Z. Luan, D. Qiu, Crocin exerts anti-proliferative and apoptotic effects on cutaneous squamous cell carcinoma via miR-320a/ATG2B, Bioengineered 12 (1) (2021) 4569–4580.
[95] A.M. D'Alessandro, A. Mancini, A.R. Lizzi, A. De Simone, C.E. Marroccella, G. L. Gravina, et al., Crocus sativus stigma extract and its major constituent crocin possess significant antiproliferative properties against human prostate cancer, Nutr. Cancer 65 (6) (2013) 930–942.
[96] D.-D. Liu, Y.-L. Ye, J. Zhang, J.-N. Xu, X.-D. Qian, Q. Zhang, Distinct pro-apoptotic properties of Zhejiang saffron against human lung cancer via a caspase-8-9-3 cascade, Asian Pac. J. Cancer Prev. 15 (15) (2014) 6075–6080.
[97] R. Hoshyar, S.Z. Bathaie, M. Sadeghizadeh, Crocin triggers the apoptosis through increasing the Bax/Bcl-2 ratio and caspase activation in human gastric adenocarcinoma, AGS, cells, DNA Cell Biol. 32 (2) (2013) 50–57.
[98] Zhao P., Luo C., Wu X., Hu H., Lv C., Ji H. Proliferation apoptotic influence of crocin on human bladder cancer T24 cell line. Zhongguo Zhong yao za zhi= Zhongguo zhongyao zazhi= China journal of Chinese materia medica. 2008;33 (15):1869–1873.
[99] S. Mahdizadeh, G. Karimi, J. Behravan, S. Arabzadeh, H. Lage, F. Kalalinia, Crocin suppresses multidrug resistance in MRP overexpressing ovarian cancer cell line, DARU J. Pharm. Sci. 24 (1) (2016) 1–8.
[100] M. Ashrafi, S.Z. Bathaie, S. Abroun, M. Azizian, Effect of crocin on cell cycle regulators in N-nitroso-N-methylurea-induced breast cancer in rats, DNA Cell Biol. 34 (11) (2015) 684–691.
[101] R.R. Hire, S. Srivastava, M.B. Davis, A.K. Konreddy, D. Panda, Antiproliferative activity of crocin involves targeting of microtubules in breast cancer cells, Sci. Rep. 7 (1) (2017) 1–11.
[102] B. Xing, S. Li, J. Yang, D. Lin, Y. Feng, J. Lu, et al., Phytochemistry, pharmacology, and potential clinical applications of saffron: a review, J. Ethnopharmacol. 281 (2021), 114555.
[103] J. Zińczuk, M. Maciejczyk, K. Zaręba, A. Pryczynicz, V. Dymicka-Piekarska, J. Kamińska, et al., Pro-oxidant enzymes, redox balance and oxidative damage to proteins, lipids and DNA in colorectal cancer tissue. Is oxidative stress dependent on tumour budding and inflammatory infiltration? Cancers 12 (6) (2020) 1636.
[104] P. Anaikutti, P. Makam, Dual active 1, 4-dihydropyridine derivatives: design, green synthesis and in vitro anti-cancer and anti-oxidant studies, Bioorg. Chem. 105 (2020), 104379.
[105] J. Shin, M.-H. Song, J.-W. Oh, Y.-S. Keum, R.K. Saini, Pro-oxidant actions of carotenoids in triggering apoptosis of cancer cells: a review of emerging evidence, Antioxidants 9 (6) (2020) 532.
[106] P. Lu, H. Lin, Y. Gu, L. Li, H. Guo, F. Wang, et al., Antitumor effects of crocin on human breast cancer cells, Int. J. Clin. Exp. Med. 8 (11) (2015) 20316.
[107] A.E. Khodir, E. Said, H. Atif, H.A. ElKashef, H.A. Salem, Targeting Nrf2/HO-1 signaling by crocin: role in attenuation of AA-induced ulcerative colitis in rats, Biomed. Pharmacother. 110 (2019) 389–399.

[108] O. Sularz, A. Koronowicz, S. Smoleń, I. Kowalska, Ł. Skoczylas, M. Liszka-Skoczylas, et al., Anti-and pro-oxidant potential of lettuce (Lactuca sativa L.) biofortified with iodine by KIO 3, 5-iodo-and 3, 5-diiodosalicylic acid in human gastrointestinal cancer cell lines, RSC Adv. 11 (44) (2021) 27547–27560.
[109] N.M. Elsherbiny, N.H. Eisa, M. El-Sherbiny, E. Said, Chemo-preventive effect of crocin against experimentally-induced hepatocarcinogenesis via regulation of apoptotic and Nrf2 signaling pathways, Environ. Toxicol. Pharmacol. 80 (2020), 103494.
[110] S.H. Kim, J.M. Lee, S.C. Kim, C.B. Park, P.C. Lee, Proposed cytotoxic mechanisms of the saffron carotenoids crocin and crocetin on cancer cell lines, Biochem. Cell Biol. 92 (2) (2014) 105–111.
[111] J. Wang, Y. Ke, T. Shu, Crocin has pharmacological effects against the pathological behavior of colon cancer cells by interacting with the STAT3 signaling pathway, Exp. Ther. Med. 19 (2) (2020) 1297–1303.
[112] K. Kawabata, N.H. Tung, Y. Shoyama, S. Sugie, T. Mori, T. Tanaka, Dietary crocin inhibits colitis and colitis-associated colorectal carcinogenesis in male ICR mice, Evid. -Based Complement. Altern. Med. (2012) 2012.
[113] Y. Zhou, Q. Xu, J. Shang, L. Lu, G. Chen, Crocin inhibits the migration, invasion, and epithelial-mesenchymal transition of gastric cancer cells via miR-320/KLF5/HIF-1α signaling, J. Cell. Physiol. 234 (10) (2019) 17876–17885.
[114] J. Tavakkol-Afshari, A. Brook, S.H. Mousavi, Study of cytotoxic and apoptogenic properties of saffron extract in human cancer cell lines, Food Chem. Toxicol. 46 (11) (2008) 3443–3447.
[115] S. Zou, Q. Tong, B. Liu, W. Huang, Y. Tian, X. Fu, Targeting STAT3 in cancer immunotherapy, Mol. Cancer 19 (1) (2020) 1–19.
[116] F. Amerizadeh, N. Rezaei, F. Rahmani, S.M. Hassanian, R. Moradi-Marjaneh, H. Fiuji, et al., Crocin synergistically enhances the antiproliferative activity of 5–flurouracil through Wnt/PI3K pathway in a mouse model of colitis-associated colorectal cancer, J. Cell. Biochem. 119 (12) (2018) 10250–10261.
[117] D. Xia, Ovarian cancer HO-8910 cell apoptosis induced by crocin in vitro, Nat. Prod. Commun. 10 (2) (2015), 1934578X1501000208.
[118] Z. He, Q. Zhou, K. Wen, B. Wu, X. Sun, X. Wang, et al., Huangkui lianchang decoction ameliorates DSS-induced ulcerative colitis in mice by inhibiting the NF-kappaB signaling pathway, Evid. -Based Complement. Altern. Med. (2019) 2019.
[119] S. Saber, R.M. Khalil, W.S. Abdo, D. Nassif, E. El-Ahwany, Olmesartan ameliorates chemically-induced ulcerative colitis in rats via modulating NFκB and Nrf-2/HO-1 signaling crosstalk, Toxicol. Appl. Pharmacol. 364 (2019) 120–132.
[120] J.-E. Tarride, M. Lim, M. DesMeules, W. Luo, N. Burke, D. O'Reilly, et al., A review of the cost of cardiovascular disease, Can. J. Cardiol. 25 (6) (2009) e195–e202.
[121] M.H. Talukder, W.M. Johnson, S. Varadharaj, J. Lian, P.N. Kearns, M.A. El-Mahdy, et al., Chronic cigarette smoking causes hypertension, increased oxidative stress, impaired NO bioavailability, endothelial dysfunction, and cardiac remodeling in mice, Am. J. Physiol. -Heart Circ. Physiol. 300 (1) (2011) H388–H396.
[122] C.J. Lavie, R.V. Milani, Cardiac rehabilitation and exercise training in secondary coronary heart disease prevention, Prog. Cardiovasc. Dis. 53 (6) (2011) 397–403.
[123] T. Gustafsson, H. Ameln, H. Fischer, C. Sundberg, J. Timmons, E. Jansson, VEGF-A splice variants and related receptor expression in human skeletal muscle following submaximal exercise, J. Appl. Physiol. 98 (6) (2005) 2137–2146.
[124] K.-C. Huang, W.-T. Wu, F.-L. Yang, Y.-H. Chiu, T.-C. Peng, B.-G. Hsu, et al., Effects of freshwater clam extract supplementation on time to exhaustion, muscle damage, pro/anti-inflammatory cytokines, and liver injury in rats after exhaustive exercise, Molecules 18 (4) (2013) 3825–3838.
[125] T. Xu, W. Ding, X. Ji, X. Ao, Y. Liu, W. Yu, et al., Oxidative stress in cell death and cardiovascular diseases, Oxid. Med. Cell. Longev. 2019 (2019).
[126] G.R. Drummond, S. Selemidis, K.K. Griendling, C.G. Sobey, Combating oxidative stress in vascular disease: NADPH oxidases as therapeutic targets, Nat. Rev. Drug Discov. 10 (6) (2011) 453–471.
[127] T. Farkhondeh, S. Samarghandian, The effect of saffron (Crocus sativus L.) and its ingredients on the management of diabetes mellitus and dislipidemia, Afr. J. Pharm. Pharmacol. 8 (20) (2014) 541–549.
[128] A.T. Hariri, S.A. Moallem, M. Mahmoudi, B. Memar, H. Hosseinzadeh, Sub-acute effects of diazinon on biochemical indices and specific biomarkers in rats: protective effects of crocin and safranal, Food Chem. Toxicol. 48 (10) (2010) 2803–2808.
[129] X.-C. Shen, Z.-Y. Qian, Effects of crocetin on antioxidant enzymatic activities in cardiac hypertrophy induced by norepinephrine in rats, Die Pharm. - Int. J. Pharm. Sci. 61 (4) (2006) 348–352.
[130] S. Soeda, T. Ochiai, H. Shimeno, H. Saito, K. Abe, H. Tanaka, et al., Pharmacological activities of crocin in saffron, J. Nat. Med. 61 (2) (2007) 102–111.
[131] K. Feidantsis, K. Mellidis, E. Galatou, Z. Sinakos, A. Lazou, Treatment with crocin improves cardiac dysfunction by normalizing autophagy and inhibiting apoptosis in STZ-induced diabetic cardiomyopathy, Nutr., Metab. Cardiovasc. Dis. 28 (9) (2018) 952–961.
[132] H. Dariushnejad, L. Chodari, V. Ghorbanzadeh, The combination effect of voluntary exercise and crocin on angiogenic miRNAs in high-fat diet/low-dose STZ-induced type2 diabetes in rats: miR-126 and miR-210, Pharm. Sci. 26 (4) (2020) 379–385.
[133] V. Ghorbanzadeh, M. Mohammadi, H. Dariushnejad, L. Chodari, G. Mohaddes, Effects of crocin and voluntary exercise, alone or combined, on heart VEGF-A and HOMA-IR of HFD/STZ induced type 2 diabetic rats, J. Endocrinol. Investig. 39 (10) (2016) 1179–1186.
[134] E.J. Lesnefsky, Q. Chen, B. Tandler, C.L. Hoppel, Mitochondrial dysfunction and myocardial ischemia-reperfusion: implications for novel therapies, Annu. Rev. Pharmacol. Toxicol. 57 (2017) 535–565.
[135] P. Balakumar, H. Singh, M. Singh, M.B. Anand-Srivastava, The impairment of preconditioning-mediated cardioprotection in pathological conditions, Pharmacol. Res. 60 (1) (2009) 18–23.
[136] M. Bernier, D. Hearse, A. Manning, Reperfusion-induced arrhythmias and oxygen-derived free radicals. Studies with" anti-free radical" interventions and a free radical-generating system in the isolated perfused rat heart, Circ. Res. 58 (3) (1986) 331–340.
[137] M. Dianat, M. Esmaeilizadeh, M. Badavi, A.R. Samarbaf-Zadeh, B. Naghizadeh, Protective effects of crocin on ischemia-reperfusion induced oxidative stress in comparison with vitamin E in isolated rat hearts, Jundishapur J. Nat. Pharm. Prod. 9 (2) (2014).
[138] M. Esmaeilizadeh, M. Dianat, M. Badavi, A. Samarbaf-Zadeh, B. Naghizadeh, Effect of crocin on nitric oxide synthase expression in post-ischemic isolated rat heart, Avicenna J. phytomedicine 5 (5) (2015) 420.
[139] C. Zeng, H. Li, Z. Fan, L. Zhong, Z. Guo, Y. Guo, et al., Crocin-elicited autophagy rescues myocardial ischemia/reperfusion injury via paradoxical mechanisms, Am. J. Chin. Med. 44 (03) (2016) 515–530.
[140] S. Goyal, S. Arora, A. Sharma, S. Joshi, R. Ray, J. Bhatia, et al., Preventive effect of crocin of Crocus sativus on hemodynamic, biochemical, histopathological and ultrastuctural alterations in isoproterenol-induced cardiotoxicity in rats, Phytomedicine 17 (3–4) (2010) 227–232.
[141] B.M. Razavi, H. Hosseinzadeh, A.R. Movassaghi, M. Imenshahidi, K. Abnous, Protective effect of crocin on diazinon induced cardiotoxicity in rats in subchronic exposure, Chem. -Biol. Interact. 203 (3) (2013) 547–555.
[142] B. Razavi, H. Hosseinzadeh, M. Imenshahidi, M. Malekian, M. Ramezani, K. Abnous, Evaluation of protein ubiquitylation in heart tissue of rats exposed to diazinon (an organophosphate insecticide) and crocin (an active saffron ingredient): role of HIF-1α, Drug Res. 65 (11) (2015) 561–566.
[143] J. Liu, Z. Qian, Effects of crocin on cholestane-3beta-5alpha-6beta-triol-induced apoptosis and related gene expression of cultured endothelial cells, J.-CHINA Pharm. Univ. 36 (3) (2005) 254.
[144] G. Xu, Z. Gong, W. Yu, L. Gao, S. He, Z. Qian, Increased expression ratio of Bcl-2/Bax is associated with crocin-mediated apoptosis in bovine aortic endothelial cells, Basic Clin. Pharmacol. Toxicol. 100 (1) (2007) 31–35.
[145] S.-Y. He, Z.-Y. Qian, F.-T. Tang, N. Wen, G.-L. Xu, L. Sheng, Effect of crocin on experimental atherosclerosis in quails and its mechanisms, Life Sci. 77 (8) (2005) 907–921.
[146] Dianat M., Radan M. A Review on the Effective Properties of Crocin in the Management of Cardiopulmonary Dysfunction.
[147] S. Heidari, S. Mehri, H. Hosseinzadeh, Memory enhancement and protective effects of crocin against D-galactose aging model in the hippocampus of Wistar rats, Iran. J. Basic Med. Sci. 20 (11) (2017) 1250.
[148] D. Sadoughi, The effect of crocin on apoptotic, inflammatory, BDNF, Pt, and Aβ40 indicators and neuronal density of CA1, CA2, and CA3 regions of hippocampus in the model of Alzheimer suffering rats induced with trimethyltin chloride, Comp. Clin. Pathol. 28 (5) (2019) 1403–1413.
[149] J. Zhang, Y. Wang, X. Dong, J. Liu, Crocetin attenuates inflammation and amyloid-β accumulation in APPsw transgenic mice, Immun. Ageing 15 (1) (2018) 1–8.
[150] B. Naghizadeh, M.T. Mansouri, B. Ghorbanzadeh, Protective effects of crocin against streptozotocin-induced oxidative damage in rat striatum, Acta Med. Iran. (2014) 101–105.
[151] E. Tamaddonfard, A.A. Farshid, S. Asri-Rezaee, S. Javadi, V. Khosravi, B. Rahman, et al., Crocin improved learning and memory impairments in streptozotocin-induced diabetic rats, Iran. J. Basic Med. Sci. 16 (1) (2013) 91.
[152] B. Lv, F. Huo, Z. Zhu, Z. Xu, X. Dang, T. Chen, et al., Crocin upregulates CX3CR1 expression by suppressing NF-κB/YY1 signaling and inhibiting lipopolysaccharide-induced microglial activation, Neurochem. Res. 41 (8) (2016) 1949–1957.
[153] K. Bisht, K. Sharma, M.-È. Tremblay, Chronic stress as a risk factor for Alzheimer's disease: roles of microglia-mediated synaptic remodeling, inflammation, and oxidative stress, Neurobiol. Stress 9 (2018) 9–21.
[154] B. Ghadrdoost, A.A. Vafaei, A. Rashidy-Pour, R. Hajisoltani, A.R. Bandegi, F. Motamedi, et al., Protective effects of saffron extract and its active constituent crocin against oxidative stress and spatial learning and memory deficits induced by chronic stress in rats, Eur. J. Pharmacol. 667 (1–3) (2011) 222–229.
[155] N.J. Justice, The relationship between stress and Alzheimer's disease, Neurobiol. Stress 8 (2018) 127–133.
[156] P. Mecocci, C. Tinarelli, R.-J. Schulz, M.C. Polidori, Nutraceuticals in cognitive impairment and Alzheimer's disease, Front. Pharmacol. 5 (2014) 147.
[157] C. Wang, X. Cai, W. Hu, Z. Li, F. Kong, X. Chen, et al., Investigation of the neuroprotective effects of crocin via antioxidant activities in HT22 cells and in mice with Alzheimer's disease, Int. J. Mol. Med. 43 (2) (2019) 956–966.
[158] P. Wang, S. Lin, Z. Chen, Y. Jiang, J. Jiang, L. Liu, Antidepressant effects of crocin-1 from saffron in mice with chronic unpredictable mild stress-induced depression, FASEB J. 33 (S1) (2019) lb75-lb75.
[159] P. Haeri, A. Mohammadipour, Z. Heidari, A. Ebrahimzadeh-Bideskan, Neuroprotective effect of crocin on substantia nigra in MPTP-induced Parkinson's disease model of mice, Anat. Sci. Int. 94 (1) (2019) 119–127.
[160] A.S. Ahmad, M.A. Ansari, M. Ahmad, S. Saleem, S. Yousuf, M.N. Hoda, et al., Neuroprotection by crocetin in a hemi-parkinsonian rat model, Pharmacol. Biochem. Behav. 81 (4) (2005) 805–813.

[161] Ettehadi H., Mojabi SN, Ranjbaran M., Shams J., Sahraei H., Hedayati M., et al. Aqueous extract of saffron (Crocus sativus) increases brain dopamine and glutamate concentrations in rats. 2013.
[162] S.V. Rao, S.C. Yenisetti, P.S. Rajini, Evidence of neuroprotective effects of saffron and crocin in a Drosophila model of parkinsonism, Neurotoxicology 52 (2016) 230–242.
[163] Z. Rajaei, M. Hosseini, H. Alaei, Effects of crocin on brain oxidative damage and aversive memory in a 6-OHDA model of Parkinson's disease, Arq. De. neuro-Psiquiatr. 74 (2016) 723–729.
[164] G. Akbari, ali Mard S, Veisi A. A comprehensive review on regulatory effects of crocin on ischemia/reperfusion injury in multiple organs, Biomed. Pharmacother. 99 (2018) 664–670.
[165] J.R. Sarshoori, M.H. Asadi, M.T. Mohammadi, Neuroprotective effects of crocin on the histopathological alterations following brain ischemia-reperfusion injury in rat, Iran. J. Basic Med. Sci. 17 (11) (2014) 895.
[166] Vakili A., Eianali MR, Bandegi AR. The protective effects of Saffron against the oxidative damage in a transient model of focal cerebral ischemia in rats. 2011.
[167] A. Vakili, M.R. Einali, A.R. Bandegi, Protective effect of crocin against cerebral ischemia in a dose-dependent manner in a rat model of ischemic stroke, J. Stroke Cerebrovasc. Dis. 23 (1) (2014) 106–113.
[168] X. Bie, Y. Chen, X. Zheng, H. Dai, The role of crocetin in protection following cerebral contusion and in the enhancement of angiogenesis in rats, Fitoterapia 82 (7) (2011) 997–1002.
[169] K. Wang, L. Zhang, W. Rao, N. Su, H. Hui, L. Wang, et al., Neuroprotective effects of crocin against traumatic brain injury in mice: involvement of notch signaling pathway, Neurosci. Lett. 591 (2015) 53–58.
[170] M. Karami, S.Z. Bathaie, T. Tiraihi, M. Habibi-Rezaei, J. Arabkheradmand, S. Faghihzadeh, Crocin improved locomotor function and mechanical behavior in the rat model of contused spinal cord injury through decreasing calcitonin gene related peptide (CGRP), Phytomedicine 21 (1) (2013) 62–67.
[171] E. Tamaddonfard, A.A. Farshid, E. Ahmadian, A. Hamidhoseyni, Crocin enhanced functional recovery after sciatic nerve crush injury in rats, Iran. J. Basic Med. Sci. 16 (1) (2013) 83.
[172] X. Wang, G. Zhang, Y. Qiao, C. Feng, X. Zhao, Crocetin attenuates spared nerve injury-induced neuropathic pain in mice, J. Pharmacol. Sci. 135 (4) (2017) 141–147.
[173] P.A. Gerber, G.A. Rutter, The role of oxidative stress and hypoxia in pancreatic beta-cell dysfunction in diabetes mellitus, Antioxid. Redox Signal 26 (10) (2017) 501–518.
[174] H. Kaneto, N. Katakami, M. Matsuhisa, T. Matsuoka, -a. Role of reactive oxygen species in the progression of type 2 diabetes and atherosclerosis, Mediat. Inflamm. 2010 (2010), 453892.
[175] Y. Tanaka, P.O.T. Tran, J. Harmon, R.P. Robertson, A role for glutathione peroxidase in protecting pancreatic β cells against oxidative stress in a model of glucose toxicity, Proc. Natl. Acad. Sci. 99 (19) (2002) 12363–12368.
[176] J.S. Harmon, R. Stein, R.P. Robertson, Oxidative stress-mediated, post-translational loss of MafA protein as a contributing mechanism to loss of insulin gene expression in glucotoxic beta cells, J. Biol. Chem. 280 (12) (2005) 11107–11113.
[177] S.I. Sherwani, C. Aldana, S. Usmani, C. Adin, S. Kotha, M. Khan, et al., Intermittent hypoxia exacerbates pancreatic β-cell dysfunction in a mouse model of diabetes mellitus, Sleep 36 (12) (2013) 1849–1858.
[178] H.I. Marrif, S.I. Al-Sunousi, Pancreatic β cell mass death, Front. Pharmacol. 7 (83) (2016).
[179] M.A. Syed, E. Barinas-Mitchell, S.L. Pietropaolo, Y.J. Zhang, T.S. Henderson, D. E. Kelley, et al., Is type 2 diabetes a chronic inflammatory/autoimmune disease? Diabetes, Nutr. Metab. 15 (2) (2002) 68–83.
[180] K.E. Wellen, G.S. Hotamisligil, Inflammation, stress, and diabetes, J. Clin. Investig. 115 (5) (2005) 1111–1119.
[181] N. Abedimanesh, B. Motlagh, S. Abedimanesh, S.Z. Bathaie, A. Separham, A. Ostadrahimi, 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.: PTR 34 (5) (2020) 1114–1122.
[182] F. Davari, Z. Alimanesh, Z. Alimanesh, O. Salehi, S.A. Hosseini, Effect of training and crocin supplementation on mitochondrial biogenesis and redox-sensitive transcription factors in liver tissue of type 2 diabetic rats, Arch. Physiol. Biochem. (2020) 1–6.
[183] M. Badavi, S.A. Mard, M. Dianat, N. Dashtbozorgi, Crocin attenuates oxidative stress and inflammation in myocardial infarction induced by isoprenaline via PPARγ activation in diabetic rats, J. Diabetes Metab. Disord. 19 (2) (2020) 1517–1525.
[184] K. Fang, M. Gu, Crocin improves insulin sensitivity and ameliorates adiposity by regulating AMPK-CDK5-PPARγ signaling, BioMed. Res. Int. 2020 (2020), 9136282.
[185] M. Ahmadi, Z. Rajaei, M.A. Hadjzadeh, H. Nemati, M. Hosseini, Crocin improves spatial learning and memory deficits in the Morris water maze via attenuating cortical oxidative damage in diabetic rats, Neurosci. Lett. 642 (2017) 1–6.
[186] H.O. Abou-Hany, H. Atef, E. Said, H.A. Elkashef, H.A. Salem, Crocin mediated amelioration of oxidative burden and inflammatory cascade suppresses diabetic nephropathy progression in diabetic rats, Chem. Biol. Inter. 284 (2018) 90–100.
[187] V. Behrouz, G. Sohrab, M. Hedayati, M. Sedaghat, Inflammatory markers response to crocin supplementation in patients with type 2 diabetes mellitus: a randomized controlled trial, Phytother. Res.: PTR 35 (7) (2021) 4022–4031.
[188] F. Kalalinia, H. Ghasim, S. Amel Farzad, E. Pishavar, M. Ramezani, M. Hashemi, Comparison of the effect of crocin and crocetin, two major compounds extracted from saffron, on osteogenic differentiation of mesenchymal stem cells, Life Sci. 208 (2018) 262–267.
[189] B. Li, K. Qin, B. Wang, B. Liu, W. Yu, Z. Li, et al., Crocin promotes osteogenesis differentiation of bone marrow mesenchymal stem cells, Vitr. Cell. Dev. Biol. Anim. 56 (8) (2020) 680–688.
[190] F. Yousefi, F.L. Arab, M. Rastin, N.S. Tabasi, K. Nikkhah, M. Mahmoudi, Comparative assessment of immunomodulatory, proliferative, and antioxidant activities of crocin and crocetin on mesenchymal stem cells, J. Cell. Biochem. 122 (1) (2021) 29–42.
[191] M. Saharkhiz, F.E. Razavi, S.M. Riahi, M. Ayadilord, Z. Rostami, M. Naseri, An in vitro study of the effects of crocin on the modulation of DSPP, VEGF-A, HLA-G5, STAT3 and CD200 expression in human dental pulp stem cells, Cell. reprogramming 23 (4) (2021) 239–249.
[192] B. An, Y. Ma, Y. Xu, X. Liu, X. Zhang, J. Zhang, et al., Crocin regulates the proliferation and migration of neural stem cells after cerebral ischemia by activating the Notch1 pathway, Folia Neuropathol. 58 (3) (2020) 201–212.
[193] S. Ahmadi, M. Nabiuni, M. Tahmaseb, E. Amini, Enhanced neural differentiation of epidermal neural crest stem cell by synergistic effect of lithium carbonate and crocin on BDNF and GDNF expression as neurotrophic factors, Iran. J. Pharm. Res.: IJPR 20 (2) (2021) 95–106.
[194] Z. Baharvand, M. Nabiuni, M. Tahmaseb, E. Amini, S. Pandamooz, Investigating the synergic effects of valproic acid and crocin on BDNF and GDNF expression in epidermal neural crest stem cells, Acta Neurobiol. Exp. 80 (1) (2020) 38–46.
[195] D.E. Leisman, L. Ronner, R. Pinotti, M.D. Taylor, P. Sinha, C.S. Calfee, et al., Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes, Lancet Respir. Med. (2020).
[196] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, lancet 395 (10223) (2020) 507–513.
[197] S. Wang, T.Q. Le, N. Kurihara, J. Chida, Y. Cisse, M. Yano, et al., Influenza Virus—cytokine-protease cycle in the pathogenesis of vascular hyperpermeability in severe influenza. The, J. Infect. Dis. 202 (7) (2010) 991–1001.
[198] R.C. Becker, COVID-19-associated vasculitis and vasculopathy, Springer, 2020, pp. 1–13.
[199] P. Tregub, V. Kulikov, Y. Motin, A. Bespalov, I. Osipov, Combined exposure to hypercapnia and hypoxia provides its maximum neuroprotective effect during focal ischemic injury in the brain, J. Stroke Cerebrovasc. Dis. 24 (2) (2015) 381–387.
[200] N. Cárdenas-Rodríguez, C. Bandala, A. Vanoye-Carlo, I. Ignacio-Mejía, S. Gómez-Manzo, E.Y. Hernández-Cruz, et al., Use of antioxidants for the neuro-therapeutic management of COVID-19, Antioxidants 10 (6) (2021) 971.
[201] P. Liu, Y. Xie, X. Meng, J. Kang, Signal transduct, Target Ther. 4 (29) (2019), 10.1038.
[202] P. Dash, P.G. Thomas, Host detection and the stealthy phenotype in influenza virus infection, Influenza Pathog. Control-Vol. II (2014) 121–147.
[203] M. Gholami, R. Nozarnezhad, M. Motaghinejad, Hypothetical protective effects of crocin carotenoid against coronavirus-induced organ damage: the possible role of the NF-κB signaling pathway, Iran. J. Med. Sci. 46 (3) (2021) 228–229.
[204] P.S. Kwon, H. Oh, S.-J. Kwon, W. Jin, F. Zhang, K. Fraser, et al., Sulfated polysaccharides effectively inhibit SARS-CoV-2 in vitro, Cell Discov. 6 (1) (2020) 1–4.
[205] H. Zakaryan, E. Arabyan, A. Oo, K. Zandi, Flavonoids: promising natural compounds against viral infections, Arch. Virol. 162 (9) (2017) 2539–2551.
[206] M.T. Khan, A. Ali, Q. Wang, M. Irfan, A. Khan, M.T. Zeb, et al., Marine natural compounds as potents inhibitors against the main protease of SARS-CoV-2—a molecular dynamic study, J. Biomol. Struct. Dyn. 39 (10) (2021) 3627–3637.
[207] Pendyala B., Patras A. In silico screening of food bioactive compounds to predict potential inhibitors of COVID-19 main protease (Mpro) and RNA-dependent RNA polymerase (RdRp). 2020.
[208] Shaghaghi N. Molecular docking study of novel COVID-19 protease with low risk terpenoides compounds of plants. 2020.
[209] P. Kar, V. Kumar, B. Vellingiri, A. Sen, N. Jaishee, A. Anandraj, et al., Anisotine and amarogentin as promising inhibitory candidates against SARS-CoV-2 proteins: a computational investigation, J. Biomol. Struct. Dyn. (2020) 1–11.
[210] S.H. Nile, G. Kai, Recent clinical trials on natural products and traditional Chinese medicine combating the COVID-19, Indian J. Microbiol. (2020) 1–6.
[211] K.-Y. Lee, J.-W. Rhim, J.-H. Kang, Immunopathogenesis of COVID-19 and early immunomodulators, Clin. Exp. Pediatr. 63 (7) (2020) 239.
[212] A. EL Alami, A. Fattah, A. Chait, Medicinal plants used for the prevention purposes during the covid-19 pandemic in Morocco, J. Anal. Sci. Appl. Biotechnol. 2 (1) (2020) 4–11, 2-1), 2020.
[213] N. Chaachouay, A. Douira, L. Zidane, COVID-19, prevention and treatment with herbal medicine in the herbal markets of Salé Prefecture, North-Western Morocco, Eur. J. Integr. Med. 42 (2021), 101285.
[214] M.S. Arshad, U. Khan, A. Sadiq, W. Khalid, M. Hussain, A. Yasmeen, et al., Coronavirus disease (COVID-19) and immunity booster green foods: a mini review, Food Sci. Nutr. 8 (8) (2020) 3971–3976.
[215] D. Hong-Zhi, H. Xiao-Ying, M. Yu-Huan, B.-S. Huang, L. Da-Hui, Traditional Chinese medicine: an effective treatment for 2019 novel coronavirus pneumonia (NCP), Chin. J. Nat. Med. 18 (3) (2020) 206–210.
[216] K. Xu, H. Cai, Y. Shen, Q. Ni, Y. Chen, S. Hu, et al., Management of COVID-19: the Zhejiang experience, J. Zhejiang Univ. (Med. Sci.) 49 (2) (2020) 147–157.
[217] B. Benarba, A. Pandiella, Medicinal plants as sources of active molecules against COVID-19, Front. Pharmacol. 11 (2020) 1189.

[218] U.K. Caliskan, M.M. Karakus, Evaluation of botanicals as potential COVID-19 symptoms terminator, World J. Gastroenterol. 27 (39) (2021) 6551.
[219] A. Mokhtari-Zaer, M.R. Khazdair, M.H. Boskabady, Smooth muscle relaxant activity of Crocus sativus (saffron) and its constituents: possible mechanisms, Avicenna J. phytomedicine 5 (5) (2015) 365.
[220] L. Delgado-Roche, F. Mesta, Oxidative stress as key player in severe acute respiratory syndrome coronavirus (SARS-CoV) infection, Arch. Med. Res. 51 (5) (2020) 384–387.
[221] A. Khalil, D. Tazeddinova, K. Aljoumaa, Z.A. Kazhmukhanbetkyzy, A. Orazov, A. D. Toshev, Carotenoids: therapeutic strategy in the battle against viral emerging diseases, COVID-19: An Overview, Prev. Nutr. Food Sci. 26 (3) (2021) 241.
[222] M. Ghasemnejad-Berenji, Immunomodulatory and anti-inflammatory potential of crocin in COVID-19 treatment, J. Food Biochem. 45 (5) (2021), e13718.
[223] J. Du, Y. Chi, Z. Song, Q. Di, Z. Mai, J. Shi, et al., Crocin reduces Aspergillus fumigatus-induced airway inflammation and NF-κB signal activation, J. Cell. Biochem. 119 (2) (2018) 1746–1754.
[224] M. Zeinali, M.R. Zirak, S.A. Rezaee, G. Karimi, H. Hosseinzadeh, Immunoregulatory and anti-inflammatory properties of Crocus sativus (Saffron) and its main active constituents: A review, Iran. J. Basic Med. Sci. 22 (4) (2019) 334.
[225] M. Ghiasian, F. Khamisabadi, N. Kheiripour, M. Karami, R. Haddadi, A. Ghaleiha, et al., Effects of crocin in reducing DNA damage, inflammation, and oxidative stress in multiple sclerosis patients: A double-blind, randomized, and placebo-controlled trial, J. Biochem. Mol. Toxicol. 33 (12) (2019), e22410.
[226] J. Yang, S.J. Petitjean, M. Koehler, Q. Zhang, A.C. Dumitru, W. Chen, et al., Molecular interaction and inhibition of SARS-CoV-2 binding to the ACE2 receptor, Nat. Commun. 11 (1) (2020) 1–10.
[227] A.M. Husaini, K.N. Jan, G.A. Wani, Saffron: A potential drug-supplement for severe acute respiratory syndrome coronavirus (COVID) management, Heliyon (2021), e07068.
[228] J. Wang, J. Kuai, Z. Luo, W. Wang, L. Wang, C. Ke, et al., Crocin attenuates lipopolysacchride-induced acute lung injury in mice, Int. J. Clin. Exp. Pathol. 8 (5) (2015) 4844.
[229] Y. Xie, Q. He, H. Chen, Z. Lin, Y. Xu, C. Yang, Crocin ameliorates chronic obstructive pulmonary disease-induced depression via PI3K/Akt mediated suppression of inflammation, Eur. J. Pharmacol. 862 (2019), 172640.
[230] M. Dianat, M. Radan, M. Badavi, S.A. Mard, V. Bayati, M. Ahmadizadeh, Crocin attenuates cigarette smoke-induced lung injury and cardiac dysfunction by anti-oxidative effects: the role of Nrf2 antioxidant system in preventing oxidative stress, Respir. Res. 19 (1) (2018) 1–20.
[231] G. Akbari, S.A. Mard, M. Dianat, E. Mansouri, The hepatoprotective and microRNAs downregulatory effects of crocin following hepatic ischemia-reperfusion injury in rats, Oxid. Med. Cell. Longev. 2017 (2017).
[232] G. Esposito, M. Pesce, L. Seguella, W. Sanseverino, J. Lu, C. Corpetti, et al., The potential of cannabidiol in the COVID-19 pandemic, Br. J. Pharmacol. 177 (21) (2020) 4967–4970.
[233] M.S. Zaghloul, E. Said, G.M. Suddek, H.A. Salem, Crocin attenuates lung inflammation and pulmonary vascular dysfunction in a rat model of bleomycin-induced pulmonary fibrosis, Life Sci. 235 (2019), 116794.
[234] D. Zhang, B.-y Qi, W.-w Zhu, X. Huang, X.-z Wang, Crocin alleviates lipopolysaccharide-induced acute respiratory distress syndrome by protecting against glycocalyx damage and suppressing inflammatory signaling pathways, Inflamm. Res. 69 (3) (2020) 267–278.
[235] Y. Xiong, J. Wang, H. Yu, X. Zhang, C. Miao, Anti-asthma potential of crocin and its effect on MAPK signaling pathway in a murine model of allergic airway disease, Immunopharmacol. Immunotoxicol. 37 (3) (2015) 236–243.
[236] H. Yosri, W.F. Elkashef, E. Said, N.M. Gameil, Crocin modulates IL-4/IL-13 signaling and ameliorates experimentally induced allergic airway asthma in a murine model, Int. Immunopharmacol. 50 (2017) 305–312.
[237] I. Aanouz, A. Belhassan, K. El-Khatabi, T. Lakhlifi, M. El-Ldrissi, M. Bouachrine, Moroccan medicinal plants as inhibitors against SARS-CoV-2 main protease: Computational investigations, J. Biomol. Struct. Dyn. 39 (8) (2021) 2971–2979.
[238] A. Stalin, D. Lin, B. Senthamarai Kannan, Y. Feng, Y. Wang, W. Zhao, et al., An in-silico approach to identify the potential hot spots in SARS-CoV-2 spike RBD to block the interaction with ACE2 receptor, J. Biomol. Struct. Dyn. (2021) 1–16.
[239] Y.Y. Zhao, R.C. Lint, Metabolomics in nephrotoxicity, Adv. Clin. Chem. 65 (2014) 69–89.
[240] B. Naghizadeh, M.T. Boroushaki, N. Vahdati Mashhadian, M.T. Mansouri, Protective effects of crocin against cisplatin-induced acute renal failure and oxidative stress in rats, Iran. Biomed. J. 12 (2) (2008) 93–100.
[241] L.-J. Su, J.-H. Zhang, H. Gomez, R. Murugan, X. Hong, D. Xu, et al., Reactive oxygen species-induced lipid peroxidation in apoptosis, autophagy, and ferroptosis, Oxid. Med. Cell. Longev. 2019 (2019), 5080843.
[242] B. Naghizadeh, S.M.T. Mansouri, N.V. Mashhadian, Crocin attenuates cisplatin-induced renal oxidative stress in rats, Food Chem. Toxicol. 48 (10) (2010) 2650–2655.
[243] M.R. Salahshoor, M. Khashiadeh, S. Roshankhah, S. Kakabaraei, C. Jalili, Protective effect of crocin on liver toxicity induced by morphine, Res Pharm. Sci. 11 (2) (2016) 120–129.
[244] S. Samarghandian, M. Azimi-Nezhad, A. Borji, T. Farkhondeh, Effect of crocin on aged rat kidney through inhibition of oxidative stress and proinflammatory state, Phytother. Res.: PTR 30 (8) (2016) 1345–1353.
[245] M.R. Dasu, S. Ramirez, R.R. Isseroff, Toll-like receptors and diabetes: a therapeutic perspective, Clin. Sci. (Lond., Engl.: 1979) 122 (5) (2012) 203–214.