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Original Paper

A Review on the Effective Properties of Crocin in the Management of Cardiopulmonary Dysfunction

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Background: Cardiopulmonary disorders are defined as a wide range of conditions that affect the heart and respiratory system. Cardiovascular Disease (CVD) and Chronic Obstructive Pulmonary Disorder (COPD) are the leading causes of early death worldwide. Oxidative stress reflects an imbalance between the Reactive Oxygen Species (ROS) and the buffering capacity of the antioxidant defense system, which ultimately causes molecular abnormalities and cellular damage. Natural antioxidants can protect biological systems against these toxic mediators. Crocin, as the main saffron constituent, is a glycosylated carotenoid with potent anti-inflammatory and antioxidant activity. It shows several pharmacological properties, including protection against cardiovascular and pulmonary system disease, tumor cell proliferation, and neuroprotective activities. Numerous studies have shown the preventive and treatment effects of crocin on various cardiac disorders, including myocardial infarction, arrhythmias, and ischemia/reperfusion, as well as various respiratory disorders, including asthma, pulmonary fibrosis, and COPD.

Objectives: This paper reviews the documented results of studies on the beneficial effects of crocin on cardiopulmonary diseases.

Methods: The scientific papers were identified by research in Web of Science, PubMed, Scopus, and Science Direct databases. Search terms were combinations of "crocin", "cardiovascular", "pulmonary", "lung", "heart", and "natural products".

Results: Current evidence confirms that crocin is a potent preventive and therapeutic agent to decrease inflammation and oxidative damage to enhance the therapeutic outcomes in conditions related to cardiopulmonary problems.

Conclusion: These desirable properties promise the future use of crocin as a therapeutic agent in cardiovascular and respiratory diseases. However, further clinical trials and toxicological studies are needed in this regard.

Keywords: Crocin, Cardiovascular, Respiratory, Cardiopulmonary, Natural products

Introduction

Cardiovascular dysfunction as a chronic disease is one of the top three causes of death worldwide. Complications of these chronic disorders are more persistent, debilitating, and costly [1]. About 20% of heart patients also have pulmonary problems, including increased respiratory rate, excessive lung ventilation, coughing with sputum, wheezing, and marked destruction of the respiratory muscles, which disrupts the normal course of life and its quality [2]. It is now well-documented that common risk factors for cardiopulmonary diseases alone cannot justify the high prevalence of these diseases [3]. In this context, some studies have suggested the role of oxidative stress in increasing disease mortality [4]. According to the results of multiple *in vivo* and *in vitro* studies, reactive species or free radicals, including reactive oxygen and nitrogen species, are also main risk factors [5-7]. The cellular sources of these compounds have not been fully elucidated, but neutrophil myeloperoxidase, NADPH oxidase (Nicotinamide Adenine Dinucleotide Phosphate oxidase), and endothelial xanthine oxidase appear to be among the most important ones [8]. To defend against free radicals, the antioxidant system, especially the enzymes such as catalase, superoxide dismutase, and glutathione peroxidase, are activated [9].

Saffron, with the scientific name *Crocus sativus* L. and a member of the Iridaceae family, is an herbaceous plant without stems that is grown in Spain, France, Greece but grows widely in central and eastern Iran [10]. The most important compounds in saffron

are carotenoids (crocin, crocetin, alpha-carotene, lycopene, and zeaxanthin), menotropin aldehydes (picrocrocin and safranal), monoterpenoids (Croconantone), isoferons, and flavonoids [11]. Crocin ($C_{44}H_{64}O_{24}$) is one of the most valuable carotenoid compounds with various therapeutic properties. Multiple human and animal studies have documented the beneficial preventive and treatment effects of crocin against health problems [12]. Crocin has anti-hypertensive [13], anti-depressant, anti-anxiety [14], anti-seizure [15], analgesic properties, anti-inflammatory, antioxidant, memory and learning enhancement, anti-Alzheimer, anti-diabetic [16], and gastrointestinal protective properties [17]. Because of the well-known antioxidant and anti-inflammatory effects of crocin, several studies have been performed on cardiovascular and respiratory system disorders induced by oxidative stress and subsequent inflammation. In the current review article, we will focus on those studies.

Search Strategy and Information Sources

This research was conducted by two investigators in scientific papers indexed in databases of Web of Science, Scopus, Science Direct, and PubMed, and published between 2000 and 2020. The English search keywords were combinations of "crocin", "cardiovascular", "pulmonary", "lung", and "heart". The interventional studies in the human population and *in vivo* and *in vitro* studies were included. But the publications evaluating the effect of crocin on the other organs disorders and dissertations, books, abstracts of conferences and patents, were excluded.

The Protective Effect of Crocin on Cardiovascular Dysfunction Induced by Diabetes

Diabetes is one of the main reasons associated with cardiac dysfunction. The factors underlying diabetes that affects the myocardium include impaired calcium handling, mitochondrial dysfunction, oxidative stress, and inflammation. According to a combined *in vivo* and *in vitro* study on the molecular cardioprotective mechanisms of crocin on diabetes-induced heart dysfunction, the phosphorylation of 5' Adenosine Monophosphate-activated Protein Kinase (AMPK) in cardiac muscles, as a master regulator of cellular energy homeostasis, increased in response to crocin treatment. This increase will result in the normalization of autophagy indexes such as SQSTM1/p62, LC3BII/LC3BI ratio, and Beclin-1. Also, crocin showed a preventive effect on autophagy and apoptosis pathways in isolated cardiac myocytes exposed to a high concentration of glucose. These results suggested that crocin can improve the cardiac function in diabetic patients by inhibiting apoptosis and normalizing autophagy in cardiac myocytes [18]. Other studies on protective properties of crocin on cardiomyopathy following Streptozotocin (STZ)-induced type 2 diabetes revealed that crocin treatment augmented the levels of miR-126 and mir-210, which play a critical role in neoangiogenesis and inhibit cell apoptosis and rescue the cardiac system from lethal damage [19]. Moreover, in this area, the other study reported that crocin treatment increases the Vascular Endothelial Growth Factor A (VEGF-A) protein expression in heart tissue by multiple functions such as promoting endothelial cell proliferation and migration and stimulating microvascular leakage, which can lead to angiogenesis in diabetic animals [20]. Additionally, a study on aortic remodeling in the STZ-diabetic rat model indicated that crocin supplementation decreases the malondialdehyde, nitric oxide, total lipids, triglycerides, cholesterol levels and also increased Glutathione (GSH) level, Catalase (CAT), and Superoxide Dismutase (SOD) activities in the crocin-treated diabetic rats. In this context, the expression of inflammatory cytokines such as Tumor Necrosis Factor (TNF) and Interleukin-6 (IL-6) in the abdominal aorta was decreased, which leads to improved aortic remodeling [21].

Effects of Crocin on Cardiac Ischemia/Reperfusion Injuries

Cardiovascular disease, especially cardiac ischemia-induced by coronary artery stenosis, is one of the most common heart diseases. It occurs due to myocardial blood flow limitation and low heart oxygen supply. Perfusion after acute myocardial ischemia appears to be essential for saving, surviving, and maintaining ischemic heart cell function. However, reperfusion causes more cell damage and death, known as reperfusion injury, by triggering a sudden onset of oxidative reactions and local inflammatory response, leading to apoptosis and necrosis of cardiomyocytes during reperfusion [22, 23]. Cardiac arrhythmias in response to reperfusion are among the common causes of sudden cardiac death. Reactive oxygen species which are increased during the cardiac reperfusion are one of the main factors in the pathophysiology of cardiac arrhythmias [24]. In this context, an animal study on crocin effects on the cardiac reperfusion-induced arrhythmia model suggested that crocin is partially capable of suppressing ventricular arrhythmias. In this experiment, Ventricular Tachycardia (VT) defined by a run of four or more Ventricular Beat (VEB) at a rate faster than the resting sinus rate, premature VEB as a discrete and identifiable premature QRS complex (premature concerning the P wave), and Ventricular Fibrillation (VF) defined as a signal for which individual QRS deflection can no longer be distinguishable from one another. These antiarrhythmic properties may have been partially justified by enhancing CAT, SOD, and GSH activities in the crocin-treated group [25]. The experimental study on cardiac hemodynamic parameters and infarct size-in ischemia/reperfusion rat model reported that crocin significantly improved mechanical functions such as ±dp/dt (as indexes of left ventricular systolic and diastolic function), coronary flow, and left ventricular systolic pressure as well as reduced infarct size in the rat hearts [26].

In this regard, *in vitro* study on isolated heart documented that crocin can amplify the antioxidant system in cardiac tissue to prevent ischemia/reperfusion injuries [27]. Endothelial NOS (eNOS) plays a crucial role in endothelial cell proliferation. It is also an essential mediator of some endothelial growth stimulants, such as vascular endothelial growth factor and prostaglandin E2. Molecular studies show that eNOS acts as a mediator in vascular restructuring as well as a potent vasodilator. In this context, crocin pretreatment in a post-ischemic isolated rat heart showed the enhanced nitric oxide synthase expression levels in cardiac myocytes and endothelium, which suggests the NO-dependent cardiovascular protection against ischemia/reperfusion injury and preserving the heart function [28]. In *in vivo* and *in vitro* studies in which the isolated mouse heart was subjected to 30 min of myocardial ischemia followed by 12 h of reperfusion, crocin pretreatment caused a significant decrease in myocardial apoptosis/ necrosis and improvement in left ventricular function. It alleviated infarct size following ischemia/reperfusion. The neonatal mouse cardiomyocytes were subjected to 2 h of hypoxia followed by 4 h of re-oxygenation. The obtained results revealed that crocin improved autophagy

during ischemia through activation of AMP-activated Protein Kinase (AMPK) and protein kinase B (Akt) [29]. Accordingly, *in vitro* study on myocardial cell injury using low glucose and hypoxia as an ischemic model showed that the medium cells containing crocin have lower levels of Malondialdehyde (MDA), Lactate Dehydrogenase (LDH), and Creatine Kinase (CK). It also increased the level of SOD and the activity of cardiac myocytes [30]. Cardiomyocytes apoptosis in ischemia/reperfusion is mostly produced by Endoplasmic Reticulum (ER) stress. The molecular mechanism of the crocin to prevent ER-injuries was established by the I/R model after ligation of the Left Anterior Descending (LAD) coronary artery for 45 min and then reperfusion for 12 h. In this study, crocin promotes the echocardiographic indexes such as Ejection Fraction (EF) and fractional shortening (FS) through decreases in the expression of active caspase 3, C/EBP Homologous Protein (CHOP), BCL2-associated X, apoptosis regulator (Bax), and Glucose-Regulated Protein of 78 kDa (GRP78). In contrast, the expression of B-cell lymphoma 2 (Bcl-2) increased by crocin pretreatment. The results of this study documented that crocin could reduce the ER stress in cardiac ischemia/reperfusion condition by modulating the miR-34a/Sirt1/Nrf2 signaling pathway [31].

Effects of Crocin on Cardiotoxicity

Myocardial Infarction (MI) and its consequences are among the leading causes of death in developed countries. Myocardial infarction is a complex phenomenon that affects the mechanical, electrical, structural, and biochemical properties of the circulatory system. Myocardial infarction occurs due to a long-term imbalance between myocardial oxygen supply and demand. Among the various mechanisms, the accumulation of free radicals has been implicated in the pathophysiology of acute myocardial infarction. Isoproterenol is a beta-adrenoceptor agonist that causes MI by creating an imbalance between oxidants and antioxidants in the myocardium. In the study on isoproterenol-induced cardiotoxicity, co-treatment with crocin improved the cardiac antioxidant status, histopathological, and lipid profile indexes which prevent the myocardial inflammation and maintains the hemodynamic parameters. These results suggest crocin as a preventive agent against MI [32].

Diazinon (DNZ) is one of the most widely-used organophosphate toxins used in agriculture. DNZ induces the production of free radicals and oxidative stress leading to cardiac toxicity. In this context, an experimental study showed that crocin prevented cardiac histopathological damages by decreased lipid peroxidation and CK-MB level and increased antioxidant content that attenuates the Bax/Bcl2 ratio elevation and activation of caspase 3-induced by DNZ subchronic exposure [33]. Another study using the same model also showed that crocin treatment protected cells against DZN via observing the lower protein ubiquitylation and increasing ubiquitin-Hypoxia-Inducible Factor 1 (HIF-1α), which leads to HIF-1α protein levels enhancement [34].

Doxorubicin (DOX) is one of the essential drugs in the treatment of solid tumors. But it leads to heart toxicity by producing free radicals and reducing the activity of the antioxidant system. One experimental study reported that crocin treatment dose-dependently showed the cardioprotective properties against DOX-induced cardiotoxicity, approved by improved ECG profile and cardiac function. In this study, crocin treatment restored the balance between oxidant-antioxidant factors and also decreased the proinflammatory cytokines. Moreover, the levels of cardiac troponin T, Aspartate aminotransferase (AST), and LDH reverted approximately to the normal values [35].

Salmonella typhimurium is a Gram-negative bacillus that belongs to the genus *Salmonella* and the family Enterobacteriaceae. This bacterium causes intestinal or extra-intestinal infections in humans, livestock, and birds. Transmission of *Salmonella* Typhimurium infections occurs following food and beverage intake. The most important pathogen of this bacterium is its Lipopolysaccharide (LPS). LPS in the bloodstream leads to the secretion of inflammatory cytokines, including the Tumor Necrosis Factor (TNF). Systemic secretion of TNF-α causes vasodilatation and decreased plasma volume, increased vascular permeability, shock, and diffuse intravascular coagulation. Endotoxic shock is also triggered by TNF-α and causes failure of vital organs, especially the heart. In an *in vitro* study based on the anti-inflammatory properties of crocin, the H9C2 cells were exposed to LPS with or without crocin co-treatment for 24 h. The obtained results demonstrated that crocin could act against LPS-induced cardiomyocyte toxicity by increasing cardiomyocyte viability, antioxidant enzyme level, NO production, and decrease in the gene expression of inflammatory cytokines such as IL-6, TNF-α, IL-1β, and PGE2 [36]. These results support the protective role of crocin in the prevention of cardiotoxicity. In this context, another *in vitro* study on cardiotoxicity using Patulin (PAT), crocin pretreatment, prevented cardiac dysfunction by Creatine Phosphokinase (CPK) levels reduction, restoring the antioxidant and redox statute, and suppressing apoptosis [37]. Similar to the mentioned studies, the results of *in vivo* study conducted on Balb/C mice using the Zearalenone (ZEN)-induced cardiotoxicity model revealed that combined treatment of various concentrations of crocin and ZEN showed a significant reduction in the apoptosis process of cardiac tissue. In this study, biochemical parameters such as intracellular enzymes (AST and ALT) and CPK, as sensitive markers for assessing damage to the heart muscle, decreased in the crocin-treatment groups. One of the critical signs of irreversible oxidative damage is protein carbonylation, which mostly damages protein function and has long-lasting harmful effects on cells and tissues. This study also identified that crocin treatment caused a significant decrease in the generation of protein carbonyls in heart tissue samples [38].

Isoprenaline changes hemodynamic factors and left ventricular dysfunction by increasing the production of free radicals, and excessive cytosolic calcium resulted in mitochondria damage. The injuries caused by isoprenaline-induced infarction are not permanent, and instead, oxidative damage due to reperfusion leads to cardiac cell death. In a study using a myocardial fibrosis model induced by isoprenaline, the administration of crocin significantly improved the electrocardiogram parameters and hydroxyproline content in the myocardial tissues, which preserved the normal heart morphology. Crocin treatment downregulated the proinflammatory cytokines (IL-1, IL-6, TNF-α, NF-κB, and TLR4) expression, associated with a remarkable decrease in transforming growth factor-β1 and connective tissue growth factor mRNA levels. These results demonstrated that crocin has potential against myocardial fibrosis through TLR4/NF-κB (p65) signal transduction pathway [39].

Effects of Crocin on Lipid Profile

Coronary artery disease results from the accumulation of athermanous plaques within the artery walls. It can be due

to the accumulation of lipids and low-density lipoproteins (LDL-C) and leukocytes' activity. This disease leads to 17.3 million deaths worldwide and accounting for approximately 31.5% of all deaths worldwide in 2017 [40]. High serum concentrations of total cholesterol, LDL-C, High-density lipoprotein (HDL-C), and triglycerides are among the risk factors for cardiovascular disease. Several studies have focused on reducing the consumption of saturated fatty acids in these patients because their high consumption causes an increase in LDL-C levels and cardiovascular dysfunction [41, 42]. According to epidemiological studies, the association between elevated serum lipids and cardiovascular disease is very strong. Decreased HDL-C levels and high triglyceride levels are directly related to increased morbidity and mortality [43, 44]. *In vivo* study on the effectiveness of crocin on the lipid profile in an STZ-induced diabetic model revealed that administration of 50 and 100 mg/kg of crocin caused a remarkable decrease in the levels of triglyceride, total cholesterol, and low-density lipoprotein, which was in line with enhanced high-density lipoprotein in the diabetic rats [45]. Another study using a high-fat diet model to evaluate the anti-obesity effect of crocin showed that oral administration of crocin in 40 and 80 mg/kg dose for 8 weeks resulted in a significant loss of body weight gain, which was associated with a remarkable decrease in plasma levels of total cholesterol and triacylglycerol [46]. Also, in this context, the results of an experiment on the preventive effect of crocin against cardiovascular dysfunction secondary to the metabolic syndrome disorder showed that 50 mg/kg crocin administration for 10 weeks showed improvement of the electrocardiogram and histological parameters leading to the amelioration of the vascular impairment in metabolic syndrome model. In this study, crocin administration preserved the normal levels of lipid profile parameters approximately at the normal levels [47]. Moreover, the *in vivo* study also confirmed that crocin suppressed the diabetes-increased lipid profile in 10, 20, 30 mg/kg doses, which was in line with decreasing IL-6 and TNF-α gene expression in rat abdominal aorta [48].

Effects of Crocin on Pulmonary Disease

Pulmonary Arterial Hypertension (PAH) is a chronic disease with a progressive increase in pulmonary artery resistance that eventually leads to a rise in right ventricular workload, failure, and sudden death. The pathogenesis of PAH involves a combination of processes of inflammation, changes in the structure of pulmonary arteries, and thrombosis with dysfunction of cellular pathways and imbalance of mediators affecting arteries. Monocrotalin is a pyrrolizidine alkaloid that causes an increase in free radicals (ROS) and severe inflammatory responses, such as a progressive increase in monocytes accumulation in the pulmonary arteries, leading to rapid signs of pulmonary hypertension. In the *in vivo* study on the rat model of PAH-induced by monocrotaline, co-treatment with crocin demonstrated the improvement of hemodynamic parameters such as right ventricular systolic pressure and cardiac hypertrophy in all concentration groups. According to the obtained data, the suggested molecular mechanism of crocin to prevent the establishment of PAH is an increase in Oxidation Resistance 1 (OXR1) expression and its downstream target genes (antioxidant enzymes) as the main defense system against oxidative stress condition [49].

Pulmonary fibrosis is a progressive and chronic disease with an average survival of 3-5 years after diagnosis. This disease can result from an imbalance between the normal process of synthesis and decomposition of extracellular matrix components. Matrix Metalloproteinases (MMPS), especially MMP-2, are family members of proteolytic enzymes that break down the extracellular matrix and basement membrane and play an essential role in developing pulmonary fibrosis. This condition is caused by the inflammation of the lung parenchyma due to inflammatory factors and is resistant to medical treatment. Bleomycin (BLM) is a well-known chemotherapy agent effective against a wide range of human cancers. BLM has the minimum toxic effect on hematopoietic tissues and the immune system, but unfortunately, due to the complication of pulmonary fibrosis, the use of this drug is limited. As regards, the experimental study using intra-tracheal instillation of BLM, the significant biochemical, structural, and pulmonary dysfunction symptoms of pulmonary fibrosis established in rats which were associated with oxidative stress condition and enhanced inflammatory process. Administration of crocin in this study showed anti-inflammatory and anti-fibrotic properties which are resulted from downregulation of IL-10 and TLR4 in lung tissue as the main pathway implicated in the anti-inflammatory properties and also downregulation of TNF-α and TGF-β1 as the main pathways involved in the anti-fibrotic activities and finally modulation of Nrf2/HO^{-1} signaling pathways as the main key regulator involved in the antioxidant defense system [50].

Chronic Obstructive Pulmonary Disease (COPD) is a progressive and incurable disease. This condition is the most common cause of death and disability due to respiratory dysfunction, characterized by permanent airflow limitation. The pathophysiology of COPD includes several pathogenic processes such as inflammation, changes in cell growth, apoptosis, lack of cell regeneration, destruction of the extracellular matrix, and oxidative stress. One of the most critical risk factors for COPD in developing countries is smoking. Smoking is accounted for the cause of 80%-90% of cases of COPD. In an *in vivo* study on chronic cigarette smoke exposure-induced lung injuries model, which focused on oxidative stress condition, crocin co-treatment as an Nrf2 activator agent showed improved Nrf2/PKC/PI3K/MAPK signaling pathway in lung tissues. It was associated with the enhanced antioxidant level target and resulted in the prevention of severe lung injuries in response to cigarette smoke [51]. In this context, other *in vitro* studies on the cytotoxicity of cigarette smoke extract in the medium of alveolar epithelial cells (A549) showed that crocin co-treatment increases the cell viability, GSH biosynthesis, and glutamate-cysteine ligase and *Nrf2* gene expression, which was associated with diminished production of reactive oxygen species [52]. These results provide evidence for the beneficial effects of daily crocin supplementation for smokers to prevent respiratory disease.

Acute Respiratory Distress Syndrome (ARDS) is one of the most serious respiratory failure conditions characterized by severe inflammation in the lungs. It has a high mortality rate. ARDS has no proven pharmacological treatment. An *in vivo* and *in vitro* study was conducted to understand the pharmacological basis of crocin treatment in ARDS using the LPS-induced acute respiratory distress syndrome model. In the *in vitro* part, the human umbilical vein endothelial cells were exposed to LPS in the presence or absence of different doses of crocin. Also, in *in vivo* part, the mice were injected intraperitoneally with the LPS. According to the results, crocin preserves the pulmonary

vascular permeability by suppressing the inflammatory process, such as a decrease in the mitogen-activated protein kinase and NF-κB levels in both *in vivo* and *in vitro* experiments. Moreover, crocin inhibited the degradation of syndecan-4 and endothelial glycocalyx heparan sulfate via downregulation of cytotoxic T cell (CTL), heparanase, and MMP-9 expressions *in vivo* and *in vitro* [53]. Along with the mentioned study, in another experiment on an animal model of acute lung injury induced by LPS, crocin administration caused a significant decrease in the IL-1β and TNF-α concentration in bronchoalveolar lavage fluid, which was associated with reducing lung edema index and improved lung histology [54].

Allergic asthma is an inflammatory disease of the respiratory system characterized by an increase in the inflammatory cells function and the secretion of inflammatory cytokines. These factors raise the levels of free radicals and the oxidative stress process. Inflammation and oxidative stress in the respiratory system cause bronchial obstruction, airway hyperresponsiveness, and mucus overproduction in the airways. Ovalbumin (OVA) is a chicken protein allergen mainly found in egg white. It is commonly used to sensitize immune reactions like allergic asthma. OVA challenge to sensitized rats enhances the number of immune cells in bronchoalveolar lavage fluid. The results of a study to evaluate the anti-asthmatic potential of crocin on OVA-induced allergic asthma showed significant suppression of pulmonary inflammation with preserving the oxidant/antioxidant homeostasis. Also, histopathological assessment demonstrated remarkable lung improvement in response to crocin treatment. These results suggest crocin as an alternative herbal drug to alleviate allergic asthma progression [55]. Along with this study, another experiment presented evidence for the suppressive effect of crocin on MAPK signaling pathways in the OVA asthmatic model. The results showed that crocin significantly inhibited airway inflammation and hyper-reactivity by decreasing the levels of IL-5, IL-13, IL-4 and suppressing the expression of lung eotaxin, p-p38, p-JNK, and p-ERK in the OVA-challenged mice [56].

Conclusion

Crocin as an alternative herbal therapy presents preventive and therapeutic effects with an anti-inflammatory and antioxidant mechanism of action that appears to treat various conditions related to cardiopulmonary reactions. These desirable properties promise the future use of crocin as a therapeutic agent in cardiovascular and respiratory diseases. However, more clinical trials and toxicological studies are needed in this regard.

Conflicts of Interest

The authors declared no conflict of interest.

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