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A comprehensive review on regulatory effects of crocin on ischemia/reperfusion injury in multiple organs

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ABSTRACT

Ischemia-reperfusion (I/R) injury affects o_2-dependent organs including liver, kidneys, heart, brain, and intestine. I/R injury is described as the cellular injury in an organ caused by ischemia and then further aggravated during the reperfusion due to intracellular alterations. It is a process that happens in clinical settings such as organ transplantation, reperfusion after thrombolytic therapy, and coronary angioplasty. Crocus sativus L. known as saffron used in folk medicine for its beneficial effects. It contains multiple bioactive compounds including the crocin, crocetin, picrocrocin, and safranal. Crocin, a water-soluble carotenoid has antitumor, radical scavenging, anti hyperlipidemia and memory improving effects. Moreover, crocin has antioxidant, and protective effects on I/R models in rats at various organs such as heart, brain, kidney, stomach, liver, and kidney as described in detail in this review.

1. Introduction

Ischemia-reperfusion (I/R) injuryis described as the dynamic phenomenon which cellular injury in an organ caused by ischemia and then further aggravated during the re-oxygenation [1].

It mainly affects o_2-dependent organs including liver, kidneys, stomach, heart, brain, and intestine [2]. It frequently occurs in clinical settings such as organ transplantation, reperfusion after thrombolytic therapy, and coronary angioplasty [3]. It can be classified into complete or partial. Ischemia also can be described as warm or cold depending on the temperature. Generally, warm ischemia takes places at 37 °C and will be harmful for molecular and signaling pathways in cell, whereas, cold ischemia occurs at almost 4–7 °C and can have protective aspects [4].

Oxygen is necessary for adenosine triphosphate (ATP) formation via oxidative phosphorylation. During ischemia, hypoxia induces depletion of cellular ATP through abruption of phosphorylation oxidative [5]. In addition, a number of processes have been involved in the pathogenesis of ischemic induced cell injury are impairments of cell calcium homeostasis, depletion of energy reservoirs, activation of enzymes of phospholipases with formation of toxic lipid metabolites, proteases, endonucleases and production of free radicals which can be lead to oxidative damage to cellular macromolecules [6], activating the ROS-dependent processes such as inflammation [7], mitochondrial permeability transition. Moreover, activation of multiple signaling pathways including nuclear factor kappa B, C-Jun N-terminal kinase, and apoptotic signaling pathways have all been reported to be involved in the cell injury during reperfusion [2].

While many studies support that crocin is a promising I/R injury-protecting agent

a comprehensive and update review on its detailed molecular mechanisms is not published yet. Here we aim to present a comprehensive study about various mechanistic roles of crocin in I/R injury, previously examined and mentioned in the literature.

2. Overview onbiological activities of crocin

Crocus sativus L., known as saffron, is a small perennial plant from the *Iridaceae* family. The main active constituent of saffron is picrocrocin and its derivatives including safranal, flavonoid derivatives, and crocin. Crocin with the chemical formula (C44H64O24) (Fig. 1) a water soluble carotenoid is the most abundant antioxidant among active constituents of C. sativus [8].

It has been shown that crocin has numerous effects such as antioxidant, inhibition of morphine withdrawal syndrome [9], anti cerebral ischemia [10], renoprotective following liver I/R injury [11], antidote

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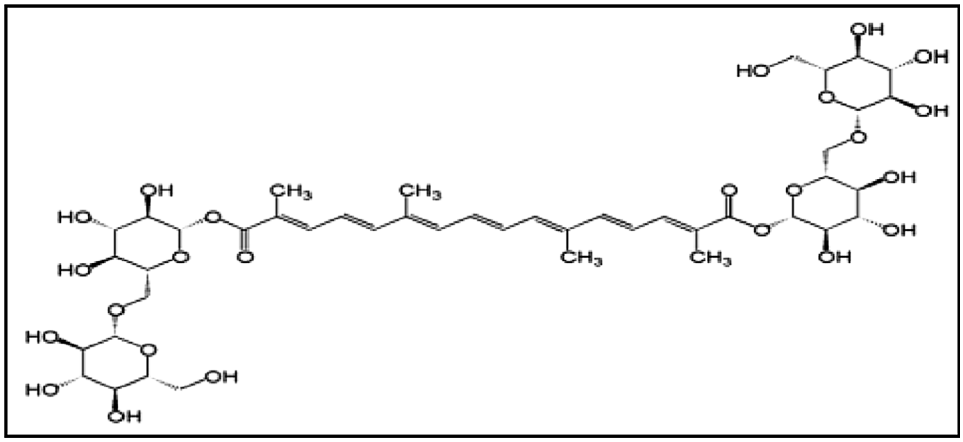

Fig. 1. Chemical structure of crocin.

Table 1
Possible mechanisms of protective effects of crocin on I/R in various organs.

Mechanisms	Organ
↑ Gene expressions of SOD and GPx, ↓MDA level, anti-apoptotic effect via ↓ Caspase 3 and anti-inflammatory activity via ↓ NO synthesisandimprovement of histopathological changes	Stomach
Up-regulating the protein expression of Nrf2; ↓levels of miR-122 and miR-34a; improving the liver enzymes of AST, ALT and ALP; ↑ the antioxidant activity of SOD, CAT, GPx, and ↓ protein expression of p53	Liver
and improvement of↑ Activity of antioxidants, ↓ MDA level, ↑ SH groups, ↓ BUN of histopathological changes	Kidney
↓ Cardiac reperfusion arrhythmias via stability or amplification of antioxidants (CAT and SOD), ↓CPK, CK-MB, and LDH, ↓ MDA level, modulatory effects on hemodynamic parameters	Heart
Anti-apoptotic via activation of the PI3K/AKT, up regulation of Bcl-2/BAX ratio, improvement of the retinal, choroid blood supply, and help to recovery of retinal	Retinal ganglion cells
Anti-edematous, ↓alterations of histopathology, ↓ERK1/2 phosphorylation, ↓ MMP-9 expression, ↓ NOS activity and NO synthesis, ↓MDA content and ↑ antioxidant capacity (SOD and GPx) and ↓ histopathological changes	Brain
Preserve viability of nerve conductivity, ↑ total SH content, ↑antioxidants capacity, ↓ MDA level and anti–inflammatory effect	Muscle

Table 2
Effects of different doses of crocin on ischemia/reperfusion injury in various organs.

Reference	Reperfusion(time)	Ischemia (time)	Dose/duration animal/route of administration	Study design	Target system
[56]	90 min	60 min	50,200,400 mg/kg prior to induction of ischemia/rat/ intraperitoinally(ip)	Ischemia/reperfusion - induced oxidative stress	kidney
[8]	30 min	10 min	20mg/kg/21days/rat/ip	Ischemia/reperfusion	Heart
[63]	60 min	30 min	10,20,40 mg/kg/21days/rat/gavage	Ischemia/reperfusion	Heart
[93]	60 min	30 min	10,20,40 mg/kg/21days/rat/gavage	Ischemia/reperfusion	Heart
[94]	1 h	2 h	50,200,400 mg/kg/1h prior to ischemia/rat/ip	Ischemia/reperfusion	Skeletal muscle
[76]	24 h	80 min	50, 80 mg/kg/ rat/ip/beginning of ischemia	Ischemia/reperfusion	Brain
[77]	24 h	20 min	5,10,20 mg/kg 21days/mice/gavage	Transient focal Ischemia-reperfusion microvessels)) cerebral	Brain
[10]	23 h	60 min	15,30,60,120 mg/kg/start of ischemia/rat/ip	Ischemia/reperfusion	Brain
[84]	Continue	60 min	5, 25, 50 mg/kg,30 min before and once daily after retinal ischemia/reperfusion injury/rat/ip	Ischemia/reperfusion	Retinal ganglion cells
[91]	3 h	30 min	7.5, 15 or 30 mg/kg/30 min before induction of ischemia/ reperfusion /ip	Ischemia/reperfusion	Stomach
[92]	3 h	30 min	15 or 30 mg/kg/30 min before induction I/R/ipof	Ischemia/reperfusion	Stomach
[20]	1 h	45 min	200mg/kg, 7 consecutive days before of induction ischemia/ reperfusion /ip	Ischemia/reperfusion	Liver

diazinon [12] and acryl amid [13], anti-hyperglycemic [14], long-term potentiation [15], anti-hyperlipidemia [16], and anti-inflammatory [17]. Furthermore, it has been reported that crocin at different doses and through multiple mechanisms exhibits beneficial effects on I/R injury in various organs such as brain [18], cardiac [19], and liver [20]. (Summarized in Tables 1 and 2).

2.1. Effects of crocin on hepatic ischemia-reperfusion injury

A series of physiological and biochemical changes occur following hepatic I/R injury. The tissue deprivation of oxygen, nutrients, and disruption of the metabolic reactions in the ischemic phase, impair mithocondrial activity which result in liver cell injury. Reperfusion in the second phase of I/R exacerbates the tissue function by activating of a series of events such as generation of ROS, activation of the inflammatory, and apoptotic mediators [21].

MicroRNAs (miRNAs, miR) are a category of internal non coding RNAs that post-transcriptionally modulate protein-coding message [22] through binding to the 3′-untranslated region (3′-UTR) of target messenger RNAs. Various studies showed that miRNAs play an important role in multiple physiological and pathological functions such as differentiation, development, and cancer [23].

miR-122, a 22 nucleotide miRNA, is derived from a RNA transcript from the gene *hcr* in the liver cells. It accounts for near 70% of total