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File: ■ Saffron (*Crocus sativus*, Iridaceae)
■ Pharmacology
■ Bioactive Apocarotenoids

HC 041851-592

Date: May 15, 2018

RE: Review of the Pharmacology of Saffron and Its Bioactive Components

Bukhari SI, Manzoor M, Dhar MK. A comprehensive review of the pharmacological potential of *Crocus sativus* and its bioactive apocarotenoids. *Biomed Pharmacother*. 2018;98:733-745.

Saffron (*Crocus sativus*, Iridaceae) dried stigmata have numerous potential therapeutic benefits. In this review, the pharmacological activities of saffron and its bioactive constituents are summarized.

Constituents
The putative active components are the apocarotenoids crocetin, crocin, safranal, and picrocrocin. A diester of the disaccharide gentiobiose and dicarboxylic acid crocetin, crocin is responsible for the intense color of saffron and is one of the few naturally occurring water-soluble carotenoids. It has antioxidant, antineoplastic, neuroprotective, and possibly antidepressant properties. The structural core of crocin, crocetin protects against retinal damage and has neuroprotective activities. Safranal has antioxidant, anticonvulsant, antineoplastic, and antidepressant properties. A precursor to safranal, picrocrocin has antioxidant and antineoplastic effects, and is used as an identity marker for saffron.

Free Radical Scavenging Activity
- Saffron aqueous extract inhibited lipid peroxidation and had free radical scavenging properties in vitro.
- Crocin and safranal decreased reactive oxygen species (ROS) production and had potent free radical scavenging activity in several in vitro models of oxidative stress.
- In vitro and in vivo studies showed that crocetin decreased plasma levels of oxidized low-density lipoprotein (LDL) (demonstrating the antioxidant effect); inhibited lipid peroxidation; increased the activity of glutathione *S*-transferases (GSTs), glutathione peroxidase (GPx), catalase, and superoxide dismutase (SOD); and decreased aryl hydrocarbon hydroxylase (AHH), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), and adenosine deaminase (ADA).
- Crocetin reduced glutathione (GSH) levels in diabetic and nondiabetic rats.

- "[T]he synergistic effect of all the bioactive constituents have been reported to contribute significantly towards the antioxidant potential of saffron."

Anticancer/Antineoplastic Effects

- Saffron extract, crocin, crocetin, and safranal suppressed proliferation of several cancer cell lines.
- In rodent models, saffron aqueous extract prevented skin carcinogenesis, soft tissue sarcomas, and hepatic cancer via inhibition of apoptosis induction and cell proliferation, modulation of oxidative damage, and suppression of inflammation.
- In mice, saffron aqueous extract and safranal prevented drug-induced genotoxicity (genotoxicity may lead to cancer).
- Crocin inhibited xenograft growth and tumor growth, and increased survival time in rodent models of cancer.
- Crocetin inhibited the proliferation of lung cancer cells and suppressed vascular endothelial growth factor (VEGF)-induced tube formation during angiogenesis (VEGF is a promotor of tumor vascularization and growth).
- The anticancer mechanism of action may involve inhibition of DNA, RNA, and protein synthesis; induction of apoptosis; alteration of epigenetics; and modulation of cell cycle regulatory proteins.
- The authors conclude that clinical trials are needed before recommending saffron to prevent and treat cancer.

Neuroprotective Effects

- Saffron and its components have demonstrated neuroprotective effects in rodent models of focal ischemia, autoimmune encephalomyelitis, cerebral ischemia, hippocampal ischemia, and renal ischemia reperfusion.
- In rodent models of ischemic stroke, crocin inhibited oxidized reactions in microvessels, reduced malondialdehyde (MDA) levels, increased SOD and GPx activity, and reduced lipid peroxidation.
- In rodent models of memory impairment, saffron extract attenuated memory impairment and improved spatial cognitive ability.
- In rodent models of memory impairment, crocin improved spatial cognitive ability and prevented learning impairment in aged mice.
- In a rat model of Alzheimer's disease (AD), saffron improved cognition deficits.
- "[S]affron has the capacity to inhibit the aggregation and deposition of amyloid β in the human brain and prevent short-term memory problems besides being both safe and effective in mild to moderate depression in Alzheimer's disease." (No additional study details were provided.)
- In a rodent model of Parkinson's disease (PD), saffron pretreatment protected dopaminergic cells.
- In a rodent seizure model, aqueous and ethanolic extracts of saffron and safranal had anticonvulsant activity. In contrast, crocin had no benefit.
- The mechanism of action underlying the protection from ischemic neural damage and memory impairment effects may involve the antioxidant effects of saffron.
- The mechanism of action in AD and PD models may involve the interaction of saffron and its components with cholinergic, dopaminergic, and glutamatergic systems.
- The authors conclude that more in vivo studies and clinical trials are needed to evaluate the potential role of saffron and its components in the treatment of nervous system diseases.

Antidepressant and Anxiolytic Effects

- In rodent models of stress, aqueous and ethanolic extract of saffron, safranal, and crocin had a positive effect on behavior.
- In a rodent model of obsessive-compulsive disorder (OCD), crocin had a positive effect on behavior.
- In mice, aqueous extract of saffron and crocin reduced the side effects of electroshock stress.
- In rodent models, crocin and safranal exhibited antidepressant effects.
- In clinical studies, saffron extract was as effective as imipramine and fluoxetine in the treatment of mild to moderate depression. (No additional study details were provided.)
- In a clinical study of patients with metabolic syndrome, 30 mg/day of crocin improved symptoms of depression. (No additional study details were provided.)
- The authors conclude that these promising findings should be confirmed in larger, well-designed, randomized, controlled trials.

Visual Impairment

- In a rodent model of visual impairment, dietary saffron prevented the damaging effects of continuous light exposure on retina morphology and function.
- In vivo, crocin increased retina and choroid blood supply and facilitated the recovery of retinal functioning after retinal ischemia.
- Crocetin protected against retinal damage in rodent models.

Anti-arthritis Effects

- In rodent models of arthritis, saffron extract had anti-inflammatory effects.
- In vitro, crocin produced an anti-inflammatory effect by acting on the cyclooxygenase (COX) pathway and inhibiting COX1 and COX2 enzymes and inhibiting production of prostaglandin E2 (PGE2).
- Crocin inhibited matrix metalloproteinases (MMPs).
- The anti-arthritis mechanism of action of saffron and crocin may involve modulation of cartilage-deteriorating enzymes, inflammatory mediators, MMPs, and antioxidant stress.

Hypolipidemic Effects

- In hyperlipidemic rats, saffron and its components decreased elevated levels of triglycerides (TGs), total cholesterol (TC), alkaline phosphatase (ALP), aspartate transaminase (AST), alanine aminotransferase (ALT), MDA, GPx, and GSH. Saffron was more effective than its individual components.
- Crocin reduced levels of TGs, TC, LDL, and very-low-density lipoproteins (VLDLs) in hyperlipidemic rats.
- Crocetin reduced levels of TC, LDL, and TGs in vivo.
- Crocin and safranal had dose-dependent hypotensive effects in hyperlipidemic rats.

Cardioprotective Effects

- Saffron and its components were cardioprotective in animal models of heart disease.
- Crocin inhibited atherosclerosis via apoptosis in vitro.
- Saffron produced electrophysiological remodeling of the atrioventricular (AV) node during atrial fibrillation.
- Aqueous extract of saffron inhibited calcium channels in isolated guinea pig heart.

- In crocetin-fed quails, there was a decrease in cholesterol deposits in the aorta, atheroma, foam cells, and atherosclerotic lesions.
- Crocetin decreased the level of cardiac markers and increased mitochondrion potential in noradrenaline-treated cardiac myocytes.
- Crocetin reduced cholesterol levels in vivo.
- In a rodent model of cardiac hypertrophy, crocetin improved myocardial pathological and histological changes induced by norepinephrine.
- The cardioprotective mechanism of action may involve antioxidant effects.

Pulmonary Effects

- Saffron and safranal protected against lung inflammation in guinea pigs.
- Safranal reduced cough in a guinea pig model.
- Safranal may be a competitive antagonist at histamine H1 receptors.
- Saffron, safranal, and crocin significantly reduced nitric oxide (NO), inducible nitric oxide synthase (iNOS), and peroxynitrite ion generation, and prevented cytochrome c release in bronchial epithelial cells. Safranal significantly reduced oxidative stress via iNOS reduction and prevented apoptosis.

Anti-diabetes Effects

- Saffron significantly decreased blood glucose levels, glycosylated serum proteins, and levels of serum advanced glycation end products (AGEs, an initiator of diabetic encephalopathy).
- Saffron decreased oxidative stress in rats with diabetic encephalopathy.
- Crocetin prevented AGE-induced bovine endothelial cell apoptosis through ROS inhibition and calcium ion stabilization, suggesting preventive effects in diabetes-associated vascular complications.
- In rat adipocytes, crocetin alleviated free fatty acid (FFA)-induced insulin insensitivity and dysregulated messenger RNA (mRNA) expression of adiponectin, tumor necrosis factor-alpha (TNF-α), and leptin, suggesting that it may help prevent insulin resistance.

Toxicology

- According to the authors, 1.5 g/day of saffron is safe, 5 g/kg is toxic, and 20 g/kg is lethal.
- Based on in vivo studies, crocin is nontoxic and nonmutagenic at pharmacological doses, and safranal is "practically nontoxic via oral administration in both mice and rats."
- Saffron is not recommended during pregnancy because there was a report that a "continuous dosage of above 10 gm saffron was enough to cause abortion."
- Allergy can occur with high doses of saffron, but this is rare.

This review highlights the need for well-designed clinical studies that assess the clinical benefits of saffron and its components. The authors did not report sources of financial support and they did not provide a conflict of interest declaration.

—Heather S. Oliff, PhD

The American Botanical Council has chosen not to reprint the original article.