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Crocin: An Overview

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ABSTRACT: Crocin(Crocetin di-gentiobiose ester) is the chemical constituent isolated from the Saffron, the dried trifid stigma of the plant *Crocus sativus* L. and also from the fruits of Gardenia(*Gardenia jasminoides Ellis*) It is found to be effective as anti-proliferative, anti-oxidant, learning and memory enhancer, brain neurodegenerative disorder, sperm cryoconservation, biosurfactant, alzheimer disorder .It has earned a universal acceptability as a phyotherapeutical drug because of its history of safe and zero side effects. This communication deals with the phytochemistry and applications of crocin in nutritional and therapeutic purposes and significance in the real world in all aspects.

KEYWORDS: Crocin; Crocetin di-gentiobiose; *Crocus sativus*; Saffron.

INTRODUCTION

A large and increasing number of patients in the world use medicinal plants and herbs for health purpose. Therefore, scientific scrutiny of their therapeutic potential , biological properties, and safety will be useful in making wise decisions about their use[1].

Crocin(digentiobiosyl 8,8'-diapocarotene-8,8'-oate; $C_{44}H_{64}O_{24}$) belongs to a group of natural carotenoid obtained commercially from the dried trifid stigma of the culinary spice *Crocus sativus* L. It is the diester formed from the disaccharide gentiobiose and the dicarboxylic acid crocetin. It had a deep red color and formed crystals with a melting point of 186^{o}C. One of the few naturally occurring carotenoids easily soluble in water. Crocin is the chemical ingredient primarily responsible for the color of saffron. Structure of Crocin (**I**) was elucidated by Karree[2] though its presence was reported by Aschoff as long ago as the 19th centuary, is the main pigment in the saffron(approx. 80%) . With water as a stationary phase and butanol as mobile phase, Crocin(I) can be isolated in pure form from the saffron extract and directly crystallized.

SOURCE

Saffron , *Crocus sativus* Linnaeus var. autamnalis; family Iridaceae, is a stemless perennial grass plant with a round sub-soil corm of 3-5cm diameter. Each corm produces 6 to 8 leaves similar to grass weeds. Out of the single ovule ovary in the centre of the flower grows a thin style of a light yellow color which ends in a triple stigma of 2-3 cm length and bright orange-red color. It is the dried style or stigmas that or saffron the spice contain many chemical substances like carbohydrates, minerals, mucilage,

vitamins(especially riboflavin and thiamin) and pigments including crocin(**Figure 1**), anthocyanin, carotene, lycopene, and zigzantin. There is also an aromatic essence turpenic(Saffranal), and picrocrocin which give saffron its distinctive flavor.

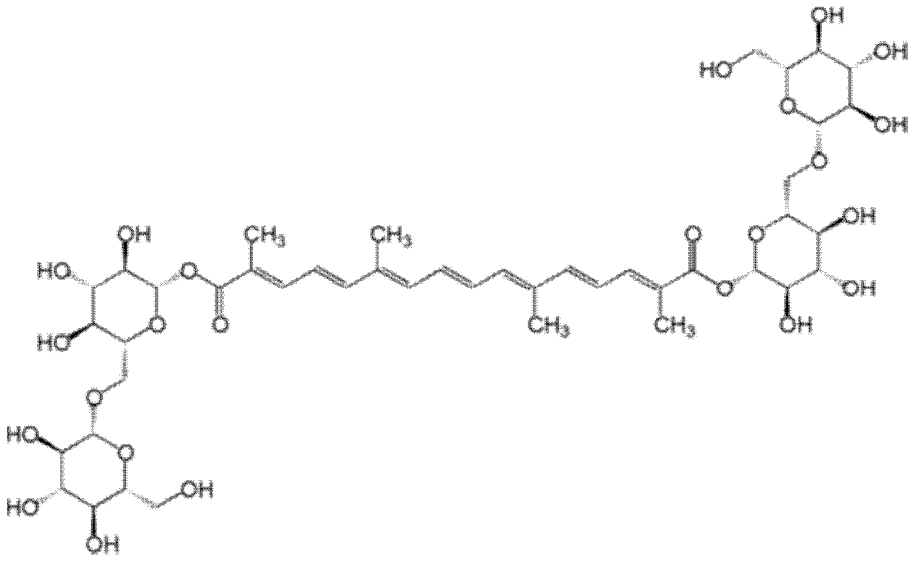

Figure 1 Structure of Crocin

Capejasmine fruit, Gardenia jasminoides Ellis, is prolate-ovoid or ellipsoid 1.5~3.5 cm long, 1~1.5 cm in diameter. The outer surface reddish-yellow or brownish-red, with 6 longitudinal winged ribs and a conspicuous longitudinal and branched vein between two ribs. Summit bearing remains of sepals, base somewhat tapering and having a remain of fruit stalk. Pericarp thin and brittle, somewhat lustrous; the inner surface relatively pale in color, lustrous, with 2~3 raised false septa. Seeds numerous, flattened ovoid, aggregated into a mass, deep red or reddish yellow, with fine and dense warts on the surface. Odor slight; slightly sour and bitter. Mainly containing gardenoside, genipin, geniposide, crocin, chlorgenic acid, gentiobioside, crocetin , gardenin, mannitol and beta-sitosterol.

WORLD PRODUCTION

Commercial saffron production occurs in Spain, Italy, Greece, Turkey, and Morocco in the Mediterranean region, Iran in Central Asia, and Kashmir and Nepal in the Himalayas. Production, albeit in very small quantities, occurs also in Australia, China, Austria, Switzerland, France, California, Myanmar, and the Argentine[3].

ABSORPTION AND BIOAVAILABILITY

Crocin is not absorbed through the gastrointestinal tract. It has been observed that orally administered crocins are hydrolysed to crocetin before or during intestinal absorption, and absorbed crocetin is partly metabolized to mono- and diglucuronide conjugates[4]. Orally administered crocin is not absorbed either after a single dose or repeated doses. It is excreted largely through the intestinal tract following oral administration. Plasma crocetin concentrations donot tend to accumulate with repeated oral doses of crocin and the intestinal tract serves as the important site for the crocin hydrolysis[5].

TOXICITY: Ames assay had indicated that crocin from saffron was nonmutagenic and nonantimutagenic[6] .

CLINICAL UTILITY

EFFECT OF CROCIN ON LEARNING AND MEMORY: Crocin has a specific, preventive effect on ethanol-induced impairment of learning and memory.

The induction of long term potentiation (LTP) in CA1 and dentate gyrus regions of the hippocampus essentially requires the activation of the N-Methyl-d-aspartate(NMDA) type of glutamate receptor. Crocin is likely to prevent ethanol induced inhibition of hippocampal LTP antagonizing the inhibitory effect of ethanol on NMDA receptor, although it is not clear whether crocin acts directly on the NMDA receptor channel complex or indirectly modulates NMDA receptor function[7].

CROCIN AS ANTIOXIDANT: Crocin scavenge free radicals, especially superoxide anions, and so may protect cells from oxidative stress. Crocin is useful as sperm cryoconservation and in protecting hepatocytes from toxins. Because of its powerful antioxidant activity, it could be useful in the therapy of neurodegenerative disorders[7-8].

CROCIN IN ALZHEIMER DISORDER: Alzheimer's disease is characterized pathologically by deposition of amyloid β-peptide (Aβ) fibrils. Oxidation is thought to promote Aβ fibril formation and deposition. To identify agents inhibiting the pathogenesis of Alzheimer's disease, in vitro the antioxidant properties of extract of *C. sativus* stigmas and its effect on $A\beta_{1-40}$ fibrillogenesis was evaluated. The antioxidant properties were determined by measuring the ferric-reducing antioxidant power and Trolox-equivalent antioxidant capacity, while its effects on Aβ-aggregation and fibrillogenesis were studied by thioflavine T-based fluorescence assay and by DNA binding shift assay. The water:methanol (50:50, v/v) extract of *C. sativus* stigmas possesses good antioxidant properties, higher than those of tomatoes and carrots, and inhibited Aβ fibrillogenesis in a concentration and time-dependent manner. The main carotenoid constituent, *trans*-crocin-4, the digentibiosyl ester of crocetin, inhibited Aβ fibrillogenesis at lower concentrations than dimethylcrocetin, revealing that the action of the carotenoid is enhanced by the presence of the sugars. The growth of research suggests the possible use of *C. sativus* stigma constituents for inhibition of aggregation and deposition of Aβ in the human brain[9].

CROCIN AND ITS PERFORMANCE AS A PHOTOSENSITIVE AGENT IN A SOLAR CELL: There are about 600 type of carotenoids on Earth, most of which are fat soluble. Out of many xanthophylls, Crocin is found to be water soluble carotenoid and the studies speculate that the Crocin has the potential to be a good photosensitive agent in an organic dye-sensitized solar cell [10].

CROCIN AS A BLEACHING AGENT FOR THE EVALUATION OF PRO-OXIDANT ACTIVITY OF FOODS BY KINETIC ANALYSIS: The pro-oxidant activity of potent oxidants and foods was determined using the kinetic analysis of crocin bleaching. In its reduced form, crocin has an absorption band at 443 nm, which disappears upon oxidation by a generic radical species. Hydroxyl radicals generated by hydrogen peroxide, peroxyl radicals from ABAP, and the stable free radical $DPPH^{\bullet}$ were allowed to react with crocin in an aqueous solution at 40 °C. Pro-oxidant activity was taken as the ratio between the decrease in crocin absorbance at 5 min and the relevant oxidant concentration [11-13].

CROCIN AS COLORING MATTER FOR FOOD AND FEED: Crocin have a long history as a coloring matter [14]. So it is oftenly used as a colorant in the dishes.

CROCIN AS SEDATIVE AND TONIC: Crocin is listed in the german Commision E monographs as a sedative to calm the nerves [3].

CROCIN EFFECTIVENESS IN COLON ADENOCARCINOMA: A growing body of research reveals that long term treatment with crocin enhances survival selectivity in female rats with colon cancer without major toxic effects. The author suggested that the selective antitumor action of crocin in female rats compared with the male might be related to hormonal factors. The effects of crocin might be related to its strong cytotoxic effect on cultured tumor cells, human and animal adenocarcinoma(HT-29 and DHD/K12-PROb cells, IC50= 0.4 and 1.0 mM, respectively) [15]. Crocin extracted from saffron , at 10mmol/L, caused cell shrinkage, widened cytoplasmic vacuole-like areas and reduced cytoplasm and pyknotic nuclei in HeLa human cervical cancer cells[16]. Crocin induced eythroid differentiation and efficiently inhibited cell growth of K562 tumor cells[17].

CROCIN AS A PRODRUG FOR ATRA-SENSITIVE CANCER: Crocetin, a metabolite of crocin, has been found to be teratogen , but far less potent than all-*trans* retinoic acid(ATRA, a chemically active form of vitamin A). This suggests that Crocin may be a safer alternative to treat ATRA-sensitive cancer in women of childbearing age with promyelocytic leukemia and other ATRA-responsive cancers [18].

CROCIN IN THE TREATMENT OF ATHEROSCLEROSIS: Adhesion and migration of the leukocyte to endothelial cells is one of the early key step in the pathogenesis of atherosclerosis and advance glycation end products(AGEs) promote this migration possibly by the expression of the intercellular adhesion molecule-1 (ICAM-1) protein. Crocetin(a metabolite of crocin) could inhibit AGE-induced bovine endothelial cells(BEC) growth suppression and significantly reduce the adhesion rate of leukocyte to BEC and also down-regulation the expression of ICAM-1 protein.[19] As crocin converts into crocetin, so probably elicit the prodrug characteristics. In addition, Crocin had protective effects on endothelial cells. Crocin could decrease CE in macrophages and uptake of Ox-LDL, inhibiting the formation of foam cell, which would promote the initiation and progression of atherosclerosis. Crocin could inhibit the [Ca2+]i elevation in smooth muscle cell, Ca2+ is an important second messenger that regulates a variety of cellular processes, including smooth muscle cell proliferation and gene expression . Crocin exerted antiatherosclerotic effects through decreasing the level of Ox-LDL that plays an important role in the initiation and progression of atherosclerosis. [20]

CROCIN AS A PRODRUG FOR THE PROPHYLACTIC TREATMENT OF AGES-INDUCED VASCULAR ENDOTHELIAL APOPTOSIS:

Advanced glycation end products (AGEs) are causally correlated with diabetic vascular complications. AGEs triggered oxidative reaction then accelerated endothelial cell apoptosis is a critical event in the process of vascular complications. Exposure of Bovine endothelial cells (BEC) to 200 g/ml AGEs for 48 h results in a significant increase in apoptotic rate, compared with control. AGEs-induced DNA fragmentation preferentially occurred in the S phase cells. Crocetin(a metabolite of crocin) prevented AGEs-induced BEC apoptosis, which correlates with crocetin attenuation of AGEs mediated increase of intracellular reactive oxygen species (ROS) formation and elevation of intracellular Ca2+ concentration ([Ca2+]i) level ($P < 0.01$ versus AGEs group). These results demonstrate that crocetin prevents AGEs-induced BEC apoptosis through ROS inhibition and [Ca2+]i stabilization and suggest that crocetin may exert a beneficial effect in preventing diabetes-associated vascular complications [21].

CROCIN AS ANTIDEPRESSANT AGENT: Crocin was reported to show antidepressant effect on mice. Crocin (50-600 mg/kg) also reduced immobility time and at dose 50 and 600, increased climbing time. Crocin may act via the uptake inhibition of dopamine and norepinephrine [22].

CROCIN AS ANTIANXIETY AGENT : Crocin administered at 50 mg/kg induced a significant increment of the latency for the first transition to the dark side and of the amount of time spent by rats in the illuminated chamber of the light/dark box. Based on the present results it could be concluded that crocins reduced the anxiety of animals exposed to the light/dark procedure without influencing rodents' motor activity. The pharmacological mechanism(s) that might account for the anxiolytic effect of crocins has yet to be determined.[23]

CROCIN AS HEPATOPROTECTIVE AGENT:

The growth of research reveals crocin as a potent hepatoprotective agent, because of its great protection in *in vivo* intoxication models in rats treated with aflatoxin B_1 and dimethylnitrosamine. The effect might be due to the hepatic tissues' defence mechanism, which elevate the cytosol glutathiones and the activities of glutathione S- transferase and glutathione peroxidase. [24-25]

CROCIN AS ANTINOCICEPTIVE AND ANTI-INFLAMMATORY AGENTS: Current research reveals that crocin exerts significant antinociceptive and anti-inflammatory activity in some models of inflammation. [26-27]

CROCIN AS APHRODISIAC AGENT: In traditional medicine, saffron is recommended as aphrodisiac agent.[28] **A**phrodisiac activity of crocin was evaluated on male rats. The growth of research reveals that the crocin elicit aphrodisiac activity by increasing mounting frequency(MF), intromission latency(IL) and ejaculation latency(EL) behaviors and reducing MF, IL and EL parameters. Crocetin, a constituent of saffron, significantly restored the EDR (endothelium-dependent relaxation) of the thoracic aorta in hypercholesterolemic rabbit, which might be explained by its action to increase the vessel eNOS activity, leading to elevation of NO production. Crocetin increased serum level of nitric oxide (NO). As crocin (the crocetin digentiobiosyl-ester) converts to crocetin, it is possible that this component acts in a way similar to PDE-5 inhibitors such as sildenafil. [29-30]

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