BBACAN-87931; No. of pages: 11; 4C: 4, 5, 6

Biochimica et Biophysica Acta xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbacan

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Review

Saffron and natural carotenoids: Biochemical activities and anti-tumor effects

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ARTICLE INFO

Article history:
Received 30 July 2013
Received in revised form 25 October 2013
Accepted 13 November 2013
Available online xxxx

Keywords:
Saffron
Natural metabolites
Carotenoids
Biochemical/immunological activities
Cancer

ABSTRACT

Saffron, a spice derived from the flower of *Crocus sativus*, is rich in carotenoids. Two main natural carotenoids of saffron, crocin and crocetin, are responsible for its color. Preclinical studies have shown that dietary intake of some carotenoids have potent anti-tumor effects both in vitro and in vivo, suggesting their potential preventive and/or therapeutic roles in several tissues. The reports represent that the use of carotenoids without the potential for conversion to vitamin A may provide further protection and avoid toxicity. The mechanisms underlying cancer chemo-preventive activities of carotenoids include modulation of carcinogen metabolism, regulation of cell growth and cell cycle progression, inhibition of cell proliferation, anti-oxidant activity, immune modulation, enhancement of cell differentiation, stimulation of cell-to-cell gap junction communication, apoptosis and retinoid-dependent signaling. Taken together, different hypotheses for the antitumor actions of saffron and its components have been proposed such as a) the inhibitory effect on cellular DNA and RNA synthesis, but not on protein synthesis; b) the inhibitory effect on free radical chain reactions; c) the metabolic conversion of naturally occurring carotenoids to retinoids; d) the interaction of carotenoids with topoisomerase II, an enzyme involved in cellular DNA-protein interaction. Furthermore, the immunomodulatory activity of saffron was studied on driving toward Th1 and Th2 limbs of the immune system. In this mini-review, we briefly describe biochemical and immunological activities and chemo-preventive properties of saffron and natural carotenoids as an anticancer drug.

Contents

1. Introduction

Natural products are of particular interest as chemo-preventive agents because of their low toxicity and potent efficacy [1]. They have long been used to prevent and treat various diseases including cancers (e.g., renal cell cancer) [2,3]. Several reports have shown that low intake of fruits and vegetables form a risk factor for chronic diseases such as cancer, coronary heart disease (CHD), stroke and cataract formation [4]. Indeed, high consumption of carotenoid-rich fruits and vegetables could offer a protective effect by increasing LDL-oxidation resistance, lowering DNA damage and inducing higher repair activity in European

Abbreviations: DMC, dimethylcrocetin; CHD, coronary heart disease; LDL, low density lipoprotein; ROS, reactive oxygen species; PCa, prostate cancer; COX-2, cycloxygenase-2; NF-κB, nuclear factor-κB; RAR, retinoid-like receptors; PPARγ, nuclear receptors effective in the differentiation of adipocytes; SXR/PXR, steroid/xenobiotic receptor/pregnane X receptor; CAR, constitutive androstane receptor; IGF-1, insulin growth factor-1; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; GJC, gap junctional communication; CD, circular dichroism; AGS, gastric adenocarcinoma; ctDNA, calf thymus DNA; MHC-I, major histocompatibility complex class I; NK-cells, natural killer cells; Th, T-helper; NO, nitric oxide; HepG-2, hepatocellular carcinoma cell line; Hep-2, laryngeal carcinoma cell line; COPD, chronic obstructive lung disease

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0304-419X/$ – see front matter © 2013 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.bbcan.2013.11.001

subjects [4]. The studies suggested that a diet characterized by a large quantity of vegetables and a great variety of both fruit & vegetable intake is associated with a reduced risk of type 2 diabetes [5]. In contrast, some studies indicated that higher intakes of specific dietary carotenoids, vitamin C, vitamin E as well as multi-vitamins were not associated with reduced risk of MS among women [6]. Intake of certain antioxidant micronutrients, particularly β-cryptoxanthin and supplemental zinc, and possibly diets high in fruits and cruciferous vegetables, could be protective against the development of rheumatoid arthritis; but, there was no association with total carotenoids, α- or β-carotene, lycopene and lutein/zeaxanthin [7]. Some studies indicated that natural products could be more effective than a dietary supplement. For example, black tea polyphenols significantly inhibited rat ovarian and human placental aromatase activities. These compounds also suppressed the proliferation in MCF-7 cancer cells [8]. On the other hand, there is a growing body of literature on the role of β-carotene and other carotenoids in human chronic diseases including cancer. Epidemiological evidence showed that a high dietary intake of fruits and vegetables rich in carotenoids is associated with a reduced risk for cancer [9]. For instance, lycopene in tomato is a powerful antioxidant which can neutralize the free radicals thereby conferring protection against macular degenerative disease; lung, bladder, cervix, skin, prostate and breast cancers; atherosclerosis and associated coronary artery diseases along with oral leukoplakia [10]. Lycopene reduces low density lipoprotein (LDL) oxidation thus reducing cholesterol levels in the blood. Its treatment has been shown to cause a 73% suppression of cellular cholesterol synthesis in J-774A.1 macrophage cell line and augment the activity of macrophage LDL receptors [10]. New reports suggest that the lycopenoids are biologically active and may reduce the risk for chronic diseases as well as influence androgen metabolism in rodent models [11]. The studies have shown that the use of lycopene in combination with other dietary agents, are the most promising treatments against cancer [12]. For example, lycopene enhances the anti-proliferative and apoptotic effects of capsaicin, the active compound in chili peppers, in in vitro prostate cancer (PCa) model. Capsaicin can induce apoptosis through the generation of reactive oxygen species (ROS), dissipation of the mitochondrial inner transmembrane potential and downstream activation of the caspase-3 cascade [12]. In addition, flavonoids are polyphenolic compounds that are abundant in fruits and vegetables. These components have anti-oxidant properties as well as anti-viral, anti-allergic, anti-inflammatory and anti-tumor activities. Flavonoids are generally classified as flavonols, flavones (e.g., apigenin and luteolin in green leafy spices), flavanones, flavanols, isoflavones or anthocyanidins based on their chemical structure [13]. Epidemiologic investigations and human clinical trials showed that flavonoids have important effects on cancer chemoprevention and chemotherapy including the treatment of mammary and prostate cancer. Flavonoids play a major role by interacting between different types of genes and enzymes. Many mechanisms of action have been identified including carcinogen inactivation, anti-proliferation, cell cycle arrest, induction of apoptosis, inhibition of angiogenesis, anti-oxidation and reversal of multi-drug resistance or a combination of these mechanisms [14]. For example, flavonoids exert their anti-inflammatory activities by inhibiting cycloxygenase-2 (COX-2) in colon cancer cells. Furthermore, they induce apoptosis and suppress the growth of colon cancer cells by inhibiting the COX-2 and Wnt/epidermal growth factor receptor/nuclear factor-κB (NF-κB) signaling pathways [13]. Recent studies have shown that some flavonoids are modulators of pro-inflammatory gene expression, thus leading to the attenuation of the inflammatory response [15].

In general, the medicinal plants are playing an important role in cancer prevention and therapy in several ways:

1. Plants represent a potential source for anti-cancer compounds. Their anti-tumor activity may result via some mechanisms such as a) effects on cytoskeletal proteins which play a key role in cell division, b) inhibition of DNA topoisomerase enzymes, c) anti-protease or antioxidant activity and d) stimulation of the immune system [16]. In this regard, natural compounds with strong anti-oxidative, hepatoprotective and anti-inflammatory effects are good candidates to evaluate their ability of influence on the initiation and growth of tumors [17].
2. Plants can delay or prevent cancer onset [16].
3. Plants can support the immune system, improving body resistance to the disease [16].
4. Plants can prevent and decrease side effects of conventional treatments [16].
5. Plants can provide nutritional and psychological support [16].

As known, several hundred theories have proposed to explain aging phenomenon. One of the most popular is the "oxidative stress theory". The endocrine system seems to have a role in the modulation of oxidative stress; however, much less is known about the role of oxidative stress in the aging of the endocrine system and the induction of age-related endocrine diseases [18]. The mechanisms such as cell senescence, mitochondrial dysfunction and microRNA dysregulation, as well as inflammation itself, can be considered to elucidate the effects of oxidative stress on aging of endocrine glands as well as the antioxidant effects of natural compounds [18]. Among natural products, saffron (*Crocus sativus* L.) stigmas are included secondary metabolites such as terpenes, flavonoids, anthocyanins and carotenoids [19]. Between them, carotenoids are the most important molecules possessing potent chemopreventive properties [20]. *C. sativus* possesses a number of medicinally important activities such as antihypertensive, anticonvulsant, antitussive, antigenotoxic and cytotoxic effects, anxiolytic aphrodisiac, antioxidant, antidepressant, antinociceptive, anti-inflammatory and relaxant activity. It also improves memory and learning skills and increases blood flow in retina and choroid [21]. Herein, we have concentrated on properties of saffron (*C. sativus* L.) and its major components especially carotenoids, as an anti-tumor compound associated with short description of other main components.

2. Saffron and its components

Saffron (*C. sativus* L.) is a species belonging to the Iridaceae family cultivated in Iran, Europe, Turkey, Central Asia, India, China and Algeria and has a wide range of activities including: a) oxytocic, b) anti-carcinogenic, c) exhilarant, d) anti-depressant and e) anti-asthma effects [22]. Saffron has been widely used as an herbal medicine, spice, food coloring and a flavoring agent since ancient times. It can increase the bioavailability and enhance absorption of other drugs [22].

Chemical analysis has shown the presence of more than 150 components in saffron stigmas [23]. *C. sativus* stigmas are characterized by the presence of sugars, minerals, fats, vitamins and secondary metabolites including terpenes, flavonoids, anthocyanins and carotenoids. Between them, carotenoids are the most important molecules because they determine color and taste of the spice [19]. From these compounds, we can mention lycopene, α- and β-carotene, zeaxanthin, crocetin (liposoluble) and crocins (hydrosoluble) derived by crocetin esterification with sugars. Crocins are *trans*-crocetin di-(β-D-gentiobiosyl) ester Q3 (named *trans*-4-GG), *trans*-crocetin (β-D-glucosyl)-(β-D-gentiobiosyl) Q4 ester (named *trans*-3-Gg), *trans*-crocetin (β-D-gentiobiosyl) ester (named *trans*-2-G), *cis*-crocetin di-(β-D-gentiobiosyl) ester (named *cis*-4-GG), *trans*-crocetin di-(β-D-glucosyl) ester (named *trans*-2-gg) and *cis*-crocetin (β-D-glucosyl)-(β-D-gentiobiosyl) ester (named *cis*-3-Gg) [19]. Crocetin is a natural carotenoid dicarboxylic acid that forms brick red crystals with a melting point of 285 °C. Its chemical structure is the central core of crocins [24]. Saffron has three main chemical constituents, which are so-called as crocin, picrocrocin and safranal. The color of saffron is due to the presence of crocin(s), which have glycoside carotenoid structure [22,25]. Crocin has a deep red color and it forms crystals with a melting point of 186 °C [24]. The bitter taste of saffron is attributed to picrocrocin [22,25].

Please cite this article as: A. Bolhassani, et al., Saffron and natural carotenoids: Biochemical activities and anti-tumor effects, Biochim. Biophys. Acta (2013), http://dx.doi.org/10.1016/j.bbcan.2013.11.001