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REVIEW ARTICLE

Role of saffron and its constituents on cancer chemoprevention

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Abstract

Context: Cancer dramatically impacts human life expectancy and quality of life. Natural substances from vegetables, herbs and spices could be beneficial in the prevention or treatment of a variety of cancers. *Crocus sativus* (Iridaceae), which has been used as a folk medicine for treating diseases for ages, showed obvious cancer chemoprevention potential.
Objective: This article focuses on the effects of *Crocus sativus* and its main ingredients, such as crocin, on cancer therapeutics.
Methods: We reviewed research data from saffron, a spice derived from the flower of *Crocus sativus*, and its constituents using the major databases, namely, Web of Science, SciFinder and PubMed.
Results and conclusion: Saffron possesses free radical-scavenging properties and antitumor activities. Significant cancer chemopreventive effects have been shown in both *in vitro* and *in vivo* models. Based on current data, saffron and its ingredients could be considered as a promising candidate for clinical anticancer trials.

Keywords

Anticancer, chemoprevention, crocin, *Crocus sativus*, cytotoxicity, dietary supplements, saffron

History

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Introduction

Cancer is one of the largest health threats to humans, claiming millions of lives each year. If cancer can be detected in its early stage, surgical intervention may be applicable as an efficacious therapeutic measure. Nevertheless, for better outcomes, many patients still need additional treatments such as chemotherapy and radiotherapy. In most cases, regular chemotherapy is unable to achieve satisfactory effects because of its severe side effects and dose-limiting toxicity. Even recently designated drug therapies with specific tumor targets are reported with many undesirable adverse effects (Venook, 2005; Wang et al., 2012). To date, no ideal approach has been found to obtain satisfactory effects against cancer.

An appropriate strategy for cancer prevention or treatment could be a combined approach, including the application of synthetic or natural agents to inhibit cancer development (Wang et al., 2012; Yang et al., 2011). Growing evidence shows that plants, such as vegetables, spices and herbs, have evolved as a solution for cancer chemoprevention and new drug development (Abdullaev, 2001; Johnson et al., 2011; Wu et al., 2012). Compared to traditional cancer therapies, natural remedies have more advantages, including little or no toxicity and low cost (Garodia et al., 2007; Lee & Park, 2003; Xu et al., 2011). Herbal medications have already been used as an alternative treatment in cancer patients (Randhawa & Alghamdi, 2011; Wang et al., 2012). On an epidemiological basis, long-term consumption of certain botanicals, such as Asian ginseng, has been associated with reduced cancer incidence (Yun et al., 2010). The anticancer effects of ginseng have also been shown in experimental studies (Attele et al., 1999; Hwang et al., 2012). Research that explores new botanical candidates with potential anticancer effects is imperative, and it supplies new data for developing safe and efficacious anticancer therapies (Hemaiswarya & Doble, 2006; Lin et al., 2012).

Crocus sativus (Iridaceae) is mainly grown in the Mediterranean Sea through Persia to India, Tibet and other regions in China. Its flower consists of various chemical constituents (Abdullaev & Espinosa-Aguirre, 2004), which have been used as a folk medicine for a long time (Figure 1). Saffron is a spice derived from the stigma of the flower of *C. sativus*, commonly known as the saffron crocus.

Saffron has been used as antispasmodic, sedative, stomachic, stimulant and emmenagogue. Saffron contains crocin, crocetin, carotene and lycopene (Giaccio, 2004), and these compounds have a variety of pharmacological effects on different medical conditions, including antitumor effects via inhibition of cell growth (Abdullaev, 1994; Aung et al., 2007). Previous studies have shown that crocetin and crocetin di-glucose ester have scavenged free radicals, especially superoxide anions, and thus protect cells from oxidative stress (Bors et al., 1982; Erben-Russ et al., 1987), responsible for many neurodegenerative disorders. Studies have also

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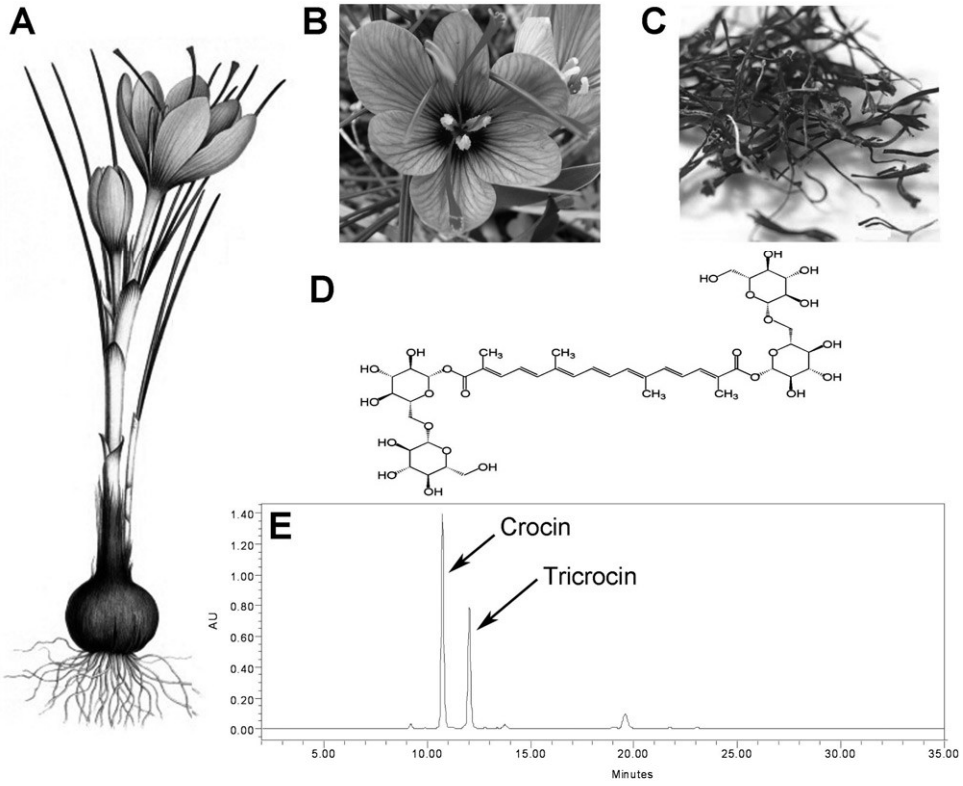

Figure 1. Botanical and phytochemical profiles of *Crocus sativus*. Morphological characteristics of *Crocus sativus* plant (A), flower (B) and stigma (C). Chemical structure of a major compound, crocin (D), and chromatogram of saffron recorded at 442 nm (E) (Aung et al., 2007).

demonstrated that saffron extract and its major constituent, crocin, may have activities against various malignancies in addition to other pharmacological activities (Abdullaev, 2003; Aung et al., 2007).

Phytochemical composition of saffron

Saffron is characterized by its specific features including bitter taste, aromatic smell and intense red color. Its bitter taste originates from picrocrocin, a β-D-glucoside of hydroxysafranal. This bitter flavored substance can be crystallized and produces glucose and aldehyde safranal by hydrolysis (Wintherhalter & Straubinger, 2000). Two of the principal coloring pigments are crocin and tricrocin (Figure 1), which are easily soluble in water. In addition to the two compounds, saffron contains crocetin as a free agent and other small amounts of pigment, such as anthocianin, α-carotene, β-carotene and zegxantin (Abdullaev, 2003; Tarantilis & Polissiou, 1997). The main aroma factor in saffron is safranal, which comprises about 60% of the volatile components of saffron. In fresh saffron, this substance exists as a stable picrocrocin. However, with heat and time it decomposes and releases the volatile aldehyde and safranal (Tarantilis & Polissiou, 1997).

Quality controlled saffron contains about 30% of crocin, 5–15% of picrocrocin and usually up to 2.5% of volatile compounds including safranal. A requirement for mature saffron is the analytical determination of picrocrocin, safranal and total crocin (Schmidt et al., 2007). The toxic effect of saffron has been found to be quite low. Animal studies indicated that the oral LD_{50} of saffron was ~20 g/kg (Abdullaev, 2003).

Cancer chemopreventive effects of saffron and its components

Studies about the effects of saffron on malignant cells have gathered attractive data. Increasing evidence indicates that saffron and its characteristic components possess antitumor activities using *in vitro* and *in vivo* models.

Cytotoxicity and cell inhibitory effects of saffron *in vitro*

Saffron had selective cytotoxic effects against tumor cells instead of healthy cells with a relatively low concentration range (Abdullaev, 2003; Schmidt et al., 2007). Incubation of HeLa cells with saffron extract resulted in obvious inhibition of colony formation and cellular DNA and RNA synthesis, with IC_{50} at 100–150 μg/ml (Abdullaev & Frenkel, 1992). A concentration-dependent inhibition of colony formation was observed in tumor cells, whereas proliferation or differentiation of normal cells remained unaffected. In another study using cancer cell lines A-549, WI-38 and VA-13 (SV-40 modified fetal lung fibroblasts), saffron extract showed much more sensitive effects on malignant cells than on normal cells. The crocetin, which was isolated from saffron, had an inhibitory effect on intracellular nucleic acid and protein synthesis in three malignant human cell lines, HeLa, A-549 and VA-13, but had no effect on colony formation (El-Daly, 1998).

Investigators have also described the growth inhibition of human chronic myelogenous leukemia cells K562 and promyelocytic leukemia cells HL-60 by dimethylcrocetin, crocetin and crocin with ID_{50} at 0.8–2.0 μM

(Morjani et al., 1990; Tarantilis et al., 1994). Cytotoxicity of dimethyl-crocetin and crocin on various cancer cell lines and human cancer cells obtained from surgical specimens (osteosarcoma, fibrosarcoma, and ovarian carcinoma) has also been reported (Nair et al., 1995).

Saffron has been found to have non-mutagenic and non-antimutagenic activities against BP-induced mutagenicity. In the *in vitro* colony formation test system, saffron displayed a concentration-dependent inhibitory effect only against human malignant cells (Abdullaev, 2003). Aung et al. (2007) demonstrated that *C. sativus* and its major constituent, crocin, significantly inhibited the growth of colorectal cancer cell lines (HCT-116, HT-29, SW-480) and non-small cell lung cancer cell line (NSCLC). However, the extract did not affect non-cancer young adult mouse colon cells (YAMC) at concentrations used to inhibit malignant cells.

Extracts of different crocus species have been shown to inhibit cell proliferation in MDA-MB-231 and MCF-7 breast cancer cell lines, and this effect was independent of the status of the estrogen receptor (Chryssanthi et al., 2007). Another study showed that saffron extract and crocetin had a clear binding capacity at the PCP binding site of the NMDA receptor and at the sigma-1 receptor, while the crocins and picrocrocin had no effective binding effect (Lechtenberg et al., 2008). Moreover, saffron extract showed inhibitory effects on the human TCC 5637 cell line and mouse fibroblast cell line (L929) (Feizzadeh et al., 2008). Subsequently, another report demonstrated that saffron extract decreased cell viability after 48-h incubation in the MCF-7 breast cancer cell line. The saffron-induced cell apoptosis was inhibited by pan-caspase inhibitor, which prompted its pro-apoptotic function (Mousavi et al., 2009).

Cancer chemopreventive effects of saffron *in vivo*

Saffron extract inhibited the initiation/promotion of 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced skin tumors in mice, delaying the onset of papilloma formation and reducing the mean number of papillomas (Salomi et al., 1991). The oral administration of the same dose of saffron extract restricted the incidence of 20-methylcholanthrene (MCA)-induced soft tissue sarcomas in mice (Salomi et al., 1991).

Extract from saffron stigmas prolonged the lifespan of cisplatin-treated mice and partially regulated the decrease in body weight, leukocyte count and hemoglobin levels (Nair et al., 1993, 1994; Salomi et al., 1991). The protective effect of administration of a combined recipe with cysteine, vitamin E and saffron extract was shown against cisplatin-induced toxicity in rats (El-Daly, 1998). It was suggested that saffron rich in carotenoids might exert its chemopreventive effects by the modulation of lipid peroxidation, antioxidants and a detoxification system. Crocetin from saffron also ameliorates bladder toxicity of the anticancer agent cyclophosphamide without altering its antitumor activity. The treatment with cysteine together with saffron extract in animals significantly reduced the toxic effects caused by cisplatin, such as nephrotoxicity and changes in enzyme activity (El-Daly, 1998; Nair et al., 1995).

Saffron treatment significantly reduced blood urea nitrogen, serum creatine level, blood glucose level and prevented many changes in serum enzyme activities. Pretreatment with the aqueous extract of saffron significantly inhibited the genotoxicity of cisplatin, cyclophosphamide, mitomycin and urethane (Premkumar et al., 2001, 2003).

Regarding the tumoricidal effects, saffron was more active by oral administration. The effect might be improved by liposome encapsulation of the drug. Liposome encapsulation of saffron produced a significant inhibitory effect on the growth of transplanted tumor cells in mice (Nair et al., 1992). Another study showed that liposome encapsulation of saffron effectively enhanced its antitumor activity against S-180 and EAC solid tumors in mice (Nair et al., 1991). Oral administration of the saffron extract increased the lifespan of mice transplanted with tumors. Further study demonstrated that crocetin was effective in treating certain types of cancer treatable with all-*trans* retinoic acids (ATRA) in frog embryos. It was suggested that crocetin might be a safe alternative to treat ATRA-sensitive cancers in women of childbearing age (Martin et al., 2002).

The effects of long-term crocin treatment were evaluated in a rat model bearing colorectal tumors, induced by DHD/K12-PROb cells (rat adenocarcinoma cell line) injected subcutaneously. Crocin significantly increased survival time and decreased tumor growth, even more intensely in females (García-Olmo et al., 1999). Saffron could play a protective role as an anti-genotoxic, antioxidant factor, which could be used as an adjuvant in chemotherapeutic medications (Premkumar et al., 2006). Evidence showed that another constituent of saffron, crotein, increased the serum level of lipid peroxidation and other marker enzymes, thus reversing the carcinogen-induced lung cancer model to near normal conditions (Magesh et al., 2006). Subsequent research showed activities of saffron and crocin on pancreatic cancer (Bakshi et al., 2010; Dhar et al., 2009) and Dalton's lymphoma (Bakshi et al., 2009) in animal models.

Mechanisms of saffron for cancer chemoprevention

Several early hypotheses of antitumor activities of saffron and its components included the inhibitory effect of saffron on cellular DNA and RNA synthesis (Nair et al., 1995), the inhibitory effect on free radical chain reactions (Tseng et al., 1995) and that the saffron extract exerted the metabolic conversion of naturally occurring carotenoids into retinoids (Bors et al., 1982; Dufresne et al., 1997). However, another report indicated that the conversion of carotenoids to vitamin A was not a prerequisite process for the anticancer activity (Smith, 1998). Relatively, it was due to the interaction of carotenoids with topoisomerase II, an enzyme involved in multicellular DNA–protein interactions. In addition, a gluco-conjugate isolated from corm and callus of saffron could cause swelling and local plasma membrane evagination, which might address that cytotoxicity was mediated via extracellular fluid uptake (Escribano et al., 1999).

Another report showed that saffron contains lectins, which suggested that the antitumor activity of saffron is mediated by lectins (Escribano et al., 1999). Treatment of tumor cells with saffron resulted in an increase in the level of intracellular sulfhydryl compounds, and chemical investigation of γ-irradiated saffron was also conducted (Zareena et al., 2001).

Recently, Amin et al. (2011) showed that saffron exerted a significant chemopreventive effect against liver cancer through inhibition of cell proliferation and induction of apoptosis. However, to date, the exact anticancer mechanisms of saffron and its main constituents are still largely unclear, and further studies are needed.

Summary and perspectives

Cancer chemoprevention, which can involve pharmacological intervention using synthetic and naturally originated agents alone or in combination, is a practical method for fighting against malignancies. Considerable evidence has suggested that plant-based dietary agents can inhibit the process of carcinogenesis effectively. Since ancient times, saffron was used as a folk medicine to treat different kinds of diseases including cancer (Li et al., 2004). A number of *in vivo* and *in vitro* experiments discussed above suggest that saffron and its main ingredients have great potential to reduce the risk of developing different types of cancer. Several monoterpenoids and a novel naturally occurring acid were isolated from the petals of saffron. Among them, three identified compounds, including crocusatin H, showed significant tyrosine inhibitory activity (Li & Wu, 2002), which could give us more opportunities to identify the effects of saffron.

Many herbal medicines with potential cancer chemopreventive effects have been reported recently (Kim et al., 2012; Lai et al., 2011; Shen et al., 2012; Zakaria et al., 2011). In addition to tumoricidal effects, anti-angiogenesis activity may also play a role in cancer chemoprevention (Lin et al., 2012). For those patients undergoing cancer chemotherapy, the efficacy and safety of botanicals has been evaluated (Yaal-Hahoshen et al., 2011; Yamaguchi et al., 2011). The effects of saffron have not yet been evaluated in human clinical trials. It would be interesting to compare the effects of saffron with other studied herbs in cancer patients. However, before saffron could be used in controlled clinical trials, more studies should be conducted, including the determination of active components in saffron and the mechanisms involved in cancer chemoprevention.

Declaration of interest

The authors declare no conflict of interest. This work was supported in part by the NIH grants P01 AT004418 and K01 AT005362.

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