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Effects of saffron and its active constituent crocin on cancer management: A narrative review

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Abstract

Background and Objective: Cancer is a major public health problem in the world, and it dramatically affects the life expectancy of patients and their quality of life. Natural products from botanicals could be beneficial in the prevention or treatment of a variety of cancers. Saffron (the extract of *Crocus sativus*) includes its major constituent, crocin, have been used as a folk medicine for a long time, and they have shown obvious cancer chemoprevention potential. The objectives of this review are to present the progress of research on the effects of saffron and crocin in cancer management and the underlying mechanisms of action.

Methods: We searched publications in the English language, published between January 1, 1980 and September 30, 2022, of saffron and crocin on cancer through several search engines, i.e., PubMed, SciFinder and Web of Science.

Key Content and Findings: In this article, we first summarize the phytochemical studies of this botanical. Then, we present the anticancer effects of saffron and crocin on different human cancer cells. Saffron and crocin showed obvious antiproliferative effects on human cancer cell lines, including colorectal cancer, breast cancer, lung cancer, prostate cancer, cervical cancer, leukemia, glioblastoma and rhabdomyosarcoma. Finally, the anticancer-related mechanisms of

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action are summarized, including cell cycle arrest at G0/G1 or G2/M phases, induction of caspase-dependent apoptosis, signaling pathway-linked tumor metabolism regulation, and adaptive immunity regulated inflammation of host immune responses.

Conclusions: Previous studies related to saffron and crocin in cancer management have been reviewed and reported results have been analyzed. Clinical data suggest that saffron and crocin have beneficial effects to improve quality of life in cancer patients. Thus, saffron and crocin can be considered promising candidates for future clinical cancer studies.

Keywords

Crocus sativus and saffron; crocin; anticancer; immune response; signaling pathway

Introduction

Cancer is a major public health problem, and this malignant disorder is a leading cause of death in the United States as well as the world (1,2). Clinically, treating cancer patients consists of several conventional medial measures, such as invasive surgery, physical radiation using controlled waves that radiate to the targeted cancerous tissue, and chemotherapy, but these methods are associated with unavoidable adverse effects on the whole body (3,4). Data in published studies showed that many cancer patients often select complementary and integrative medical means to treat cancer, reduce cancer related symptoms, and decrease adverse events associated with cytotoxic chemotherapy. Therefore, for a better clinical outcome, chemoprevention and cancer treatment may include the use of natural products or herbal medicines in addition to conventional chemotherapy to restore body homeostasis and inhibit tumor initiation, development and metastasis.

As an attractive source of novel therapeutic substances, nature boasts a tremendous chemical diversity consisting of millions of botanical species, oceanic elements, and microorganisms. Natural products have historically served as a consistent source of medical remedies. To date, more than 65% of clinically used medications are originally derived from natural products (5,6). As a matter of fact, botanical-derived lead constituents and their semi-synthetic and synthetic analogs are one major source for the development of novel anti-cancer medications. The herbal medicine source has been the mainstay of chemotherapy in the past 60 years. Several anticancer candidate compounds, such as acronyciline, bruceantin, flavopiridol, and thalicarpin, are currently under clinical evaluation (6,7).

Compared with conventional cancer treatment, natural products have their advantages, including a much lower medical expenditure and limited or no toxic effects (8,9). More than several herbal medications are currently being used as an alternative measure by patients suffering from different malignancies (10,11). Epidemiology study data suggested that long-term consumption of herbal medicines resulted in an observed significant reduction of non-specific organ related cancer incidence (12–14). Experimentally, in vitro and animal studies have demonstrated cancer chemoprevention activities of ginseng compounds and their metabolites (15,16). With newly developed high-throughput compound screening methodologies, compounds and their metabolites from natural products should supply

abundant lead structures for developing efficacious anticancer agents with reduced adverse events (17,18).

Crocus sativus is a botanical that belongs to the iris family (Iridaceae). This plant mainly grows in some Mediterranean countries, India, and some regions in China, such as Tibet. The flower of this botanical contains a number of chemical constituents with therapeutic potential (19), and has thus been used as a folk medicine for a very long time. Saffron is a component that can be used as a spice for food flavoring and coloring and is derived from the stigma of the flower of the plant commonly known as the saffron crocus.

Medicinally, saffron possesses antispasmodic, sedative, stomachic, stimulant and emmenagogue activities. Saffron contains several constituents, such as crocin, crocetin, carotene, and lycopene (20), and these compounds have different pharmacological effects suitable for addressing different medical conditions, including antitumor action via the inhibition of cancer cell growth (21,22). Crocetin and crocetin di-glucose ester can scavenge free radicals, especially superoxide anions, and therefore they can protect cells from oxidative stress associated with many neurodegenerative disorders (23,24). Furthermore, experimentally, saffron extract and crocin have demonstrated activities in preventing and treating some malignancies (25,26). The objectives of this review are to present research progress in anticancer effects of saffron and crocin and the underlying mechanisms of action. Saffron and crocin have been used as dietary supplements for a long time and should thus be considered to be generally recognized as safe. Considering their beneficial pharmacological potentials in addition to their anticancer adjuvant activities, saffron and crocin could be used as dietary supplements to improve the quality of life of cancer patients.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://lcm.amegroups.com/article/view/10.21037/lcm-21-72/rc).

Methods

This article summarized the publications from January 1, 1980 to September 30, 2022 on saffron and crocin in cancer management through several library search engines such as PubMed, SciFinder and Web of Science for over 300 journal articles in the English language. The search strategy was summarized in Table 1.

Phytochemical studies on saffron

Saffron is characterized by its individual properties, including intense red color, aromatic smell, and bitter taste. Up to now, more than 150 compounds have been isolated and identified from saffron, and have subsequently been summarized in a recently published review article (27).

The origin of saffron's bitter taste is a β-D-glucoside of hydroxysafranal, picrocrocin. After hydrolysis, this compound can be crystallized and produces glucose and aldehyde safranal (20,28). Easily soluble in water, crocin and tricrocin are two major coloring pigments in saffron.

In addition to the two compounds, saffron contains crocetin as a free agent and other small amounts of pigment, such as zeaxanthin, α-carotene, β-carotene and anthocyanin (29,30). Safranal is the major aroma factor in saffron, which comprises over 50% of saffron's volatile substances. This component exists as a stable picrocrocin in fresh saffron; however, with heating or a long period of storage, it can be decomposed to the safranal and the other volatile aldehyde (29,30).

In the market, the commonly available saffron with quality control contains crocin (about 30%), picrocrocin (5 to 15%), and volatile compounds (up to 2.5%, including safranal). Based on quantitative determination, the mature saffron should contain the required amount of total crocin, safranal, and picrocrocin (31). The toxicity data suggest that saffron is safe for humans since the LD_{50} of saffron in animals was as high as 20 g/kg (25).

Saffron and crocin on cancer management

Attractive data have been obtained from studies of the effects of saffron on different cancer cells. Using *in vitro* cells and *in vivo* animal models, more and more evidence illustrates that saffron, crocin, and other characteristic compounds possess cancer chemopreventive effects.

Cancer cell growth inhibitory effects—Saffron had antiproliferative effects against cancer cells in low concentrations without influencing the growth of healthy cells (25,31). Significant colony formation inhibition and synthesis of cellular DNA/RNA was observed by the treatment of saffron on *HeLa* cells, with relatively low IC_{50} (less than 150 μg/ml) (32). Using the doses that did not affect the growth of different normal cells, concentration-dependent cancer cell growth inhibitory effects of saffron were observed. In another study, compared to normal lung fibroblasts cells (WI-38), saffron showed much stronger effects on lung cancer cells, including A-549 and VA-13 cell lines. Crocetin, an active compound purified from saffron, did not influence colony formation, but this compound showed significant cell growth inhibitory effects on three human cancer cell lines, including *HeLa* (cervical cancer), A-549 and VA-13 (lung cancer), via regulation of intracellular DNA/RNA and protein synthesis (33). Recently, saffron and crocins were found to have antiproliferative effects on glioblastoma and rhabdomyosarcoma cells (34).

Researchers also reported the inhibitory effects of dimethylcrocetin, crocetin, and crocin on human K562 chronic myelogenous leukemia cells and HL-60 promyelocytic leukemia cells with low ID_{50}, which are less than 2 μM (35,36). Using different tumor cells and surgical specimens (ovarian carcinoma, fibrosarcoma and osteosarcoma), the anticancer activities of both crocin and a derivative of crocin (dimethylcrocetin) have also been observed (37).

Saffron has been found to have non-antimutagenic and non-mutagenic effects against mutagenicity by the induction of benzo[a]pyrene. Using an *in vitro* formation of colony model, saffron showed inhibitory effects on human tumor cells in a dose-dependent manner, and its antiproliferative potential was selective of only malignant cells (25). Crocin, the major constituent of saffron, significantly inhibited the proliferation of HCT-116, HT-29, and SW-480 human colorectal cancer cell lines, and the NSCLC human non-small cell lung cancers (22). However, the extract did not affect the growth of non-cancer normal cells at the concentrations employed to inhibit malignant cells (22).

Regarding the human breast cancer cells, using MDA-MB-231 and MCF-7 cell lines, different *Crocus* extracts have been shown to inhibit cell growth on both cell lines via the regulation of estrogen receptor expression (38). Another study showed that for the NMDA and sigma-1 receptors, saffron and crocetin can bind to the binding site of PCP. On the other hand, no similar binding effect was observed by the treatment of crocins and picrocrocin (39). In addition, using human TCC 5637 cells and mouse L929 fibroblast cells, growth-inhibitory effects of saffron were observed (40). Moreover, using MCF-7 cells, after 48 hour treatment, saffron decreased cell proliferation, and its mechanisms of antiproliferation included the induction of apoptosis, which was verified by the use of caspase inhibitors (41).

Antitumor effects in animal models—Using a skin tumor mouse model, it was observed that saffron possesses the ability to inhibit skin tumor initiation and promotion: the papilloma formation was delayed and the number of papillomas was reduced (42). Oral ingestion of saffron decreased the 20-methylcholanthrene induced skin carcinogenesis in mice (42).

Saffron increased the life span of mice treated with cisplatin and reduced the body weight decrease, the count of leukocyte, and the level of hemoglobin (42,43). Using a rat model, a combined recipe (saffron, vitamin E and cysteine) showed protective effects against cisplatin-induced toxicity (33). Data suggested that saffron's chemopreventive activities may produce these effects through a detoxification system, lipid peroxidation modulation, and antioxidant properties. Crocetin, one of the representative compounds in saffron, ameliorates the anticancer agent that works against cyclophosphamide-induced bladder toxicity without reducing its anticancer potential. In addition, saffron together with cysteine significantly inhibited the toxicity of cisplatin in an animal model, including enzyme activity changes and protection of nephrotoxicity (33,37).

Furthermore, evidence showed crotein reversed the carcinogen-induction rate in a lung cancer animal model via the regulation of marker enzymes and increased the lipid peroxidation serum level (44). Using different animal models, further studies illustrated anticancer potentials of saffron and crocin on pancreatic cancer (45,46) and Dalton's lymphoma (47).

As an active compound against cancers, crocin, the main water-soluble carotenoid of saffron, represents the most promising representative constituent of saffron extract. Using a colorectal tumor bearing rat model, the effects of long-term crocin treatment were evaluated. Long-term treatment with crocin enhances survival in rats with colon cancer without major toxic side effects (48).

Adjuvant cancer therapies—Saffron prevented serum enzyme activity changes and reduced levels of blood glucose, serum creatine, and blood urea nitrogen. Pretreatment with saffron water extract significantly inhibited cisptalin induced genotoxicity and the expression of urethane, mitomycin and cyclophosphamide (49,50).

Regarding the tumoricidal effects, saffron was more active by oral administration. The liposome encapsulation of the drug could improve the effect of saffron. A significant growth

inhibiting activity of the transplanted tumor was observed by the treatment of liposome encapsulation of saffron in mice (51). In another study, using a mouse model, we showed that saffron with liposome encapsulation increased its inhibitory effects against solid tumors (52). The life span of mice that were transplanted with tumors was increased by the treatment of oral saffron extract. Furthermore, crocetin was active in treating different types of cancers. Pharmacological and toxicity data suggested that crocetin could be a safe and active agent to inhibit ATRA-sensitive cancers in women (53).

In cancer management, the anticancer efficacy is limited by the genotoxicity of anti-tumor drugs. To test the chemoprotective potential of saffron against the genotoxicity of anticancer drugs, including mitomycin C, cyclophosphamide, and cisplatin, saffron was orally administered to the mice before the administration of anticancer drugs and the activities of saffron have been investigated. Pre-treatment of saffron inhibited anticancer agents induced damage on cellular DNA, suggesting that saffron could play a protective role as an antioxidant and anti-genotoxic agent that could be used as an adjuvant in chemotherapeutic medications (54).

Mechanisms of saffron for cancer chemoprevention

Based on published studies, the anticancer effects of saffron and crocin work through multiple mechanisms, including modulation of cell cycle progression, induction of apoptosis, regulation of tumor metabolism, and modulation immune responses.

Cell cycle arrest—The cell cycle, which causes a cell to divide into two next-generation cells, is the series of events that take place in a cell that includes the G1 phase (preparation or interphase phase) and the S phase (the DNA synthesis period), followed by the G2 (the postsynthetic gap phase) and M phase (mitosis). Cancer cells lack normal growth controls, exhibit loss of cell cycle control, have unlimited reproductive potential, and have growth-signal self-sufficiency. Any compound aimed at controlling these processes would be beneficial in suppressing cancer progression (55).

Several previous studies have suggested that the induction of cell cycle arrest is a potential anticancer mechanism for saffron. In an *in vivo* study, using a liver cancer-bearing rat model, saffron increased cell cycle arrest (56). Metastasis-associated colon cancer 1 (MACC1) is a major causal metastasis-inducing gene. Its value as a biomarker for metastasis risk has been confirmed by numerous studies. Recently, the inhibitory effects of saffron on MACC1-induced cancer cell proliferation were investigated. In an MACC1-dependent manner, saffron inhibited colon cancer cell growth and migration. Data showed that the proportion of the G2/M phases of the MACC1-expressing cells was increased by the treatment of saffron. On the other hand, for the low MACC1-expressing cells, the effects of saffron on G2/M cell cycle arrest were obviously reduced. These findings illustrated that saffron primarily induced cell cycle arrest in an MACC1-dependent manner (57).

As a major constituent in saffron, crocin inhibits tumor growth in several types of cancers, while cell cycle arrest is one of the important mechanisms in preventing cancer. The anti-leukemic effects of crocin have been investigated in a human leukemia cell line *in vitro* and *in vivo*. Experimental data showed that, in a concentration- and time-dependent manner,

crocin has cancer cell growth inhibitory effects on HL-60 cells, and G0/G1 cell cycle arrest was observed by the treatment of crocin (58). In addition, by down-regulating the expression of cyclin D1, crocin inhibited the progression of the cell cycle (59). The bioactivity of crocin on breast cancer could be related to its potential for cyclin D1 suppression and p21Cip1 up-regulation, while cell cycle arrest induced by crocin might operate in a p53-dependent manner (60).

Induction of cell apoptosis—Apoptosis is programmed cell death and is a highly regulated process used to eliminate unwanted or defective cells (61). Many chemotherapeutic agents, including natural compounds, radiation, immunotherapy, and cytokines, induce cancer cell death via the apoptotic pathway (62). Effects of saffron on p53-associated apoptosis have been observed. Using a p53 isogenic colon cancer cell model, saffron inhibited cell growth via apoptosis, which was supported by DNA damage assay (63). In addition, treatment of p53-overexpressing tumor cells with saffron resulted in cell death mediated by p53 through apoptotic mechanisms including BAX over-activation. These results suggested that, for the saffron induced apoptosis in cancer cells, p53 may play a critical role (64).

Regarding crocin, in the 1990s, using a HeLa cell model, it was observed that crocin-induced changes in morphology, including piknotic nuclei and cell shrinkage, suggesting that the cancer cell growth inhibitory effects of crocin could be mediated by apoptosis (65). The antiproliferative effects of crocin have been investigated on prostate cancer cell lines. Data suggested that crocin induces apoptosis in human prostate cancer cells, partly via an intrinsic pathway of apoptosis by activation of caspase-9 (59). Crocin triggers apoptosis via caspase activation and the ration increasing of Bax/Bcl-2 in gastric adenocarcinoma cells of humans (66). It has been demonstrated that crocin inhibited human breast cancer cell growth through apoptotic induction accompanied with extensive DNA damage. Crocin also induced breast cancer cell apoptosis via caspase-3 dependent pathways (67).

Anti-cancer drug-mediated apoptosis in cancer cells is largely regulated via an intrinsic (mitochondrial) or extrinsic (death receptor) pathway via caspase activations. In a recent study, it was found that caspase 8 activates the death receptors (extrinsic) and caspase 9 activates the mitochondrial pathway (intrinsic) to induce cancer cell apoptosis, which was observed by the treatment of crocin. The equivalent upregulation of caspases 8 and 9 suggested that both the extrinsic and intrinsic apoptotic pathway are involved in crocin-mediated cancer cell apoptosis (68).

Tumor metabolism regulation—Several early hypotheses surrounding the anticancer potential of saffron and its constituents included the suppressing effect of saffron on metabolism of cells, which includes synthesis of DNA and RNA (37), the inhibition of the free radical chain reaction (69), and the metabolic conversion of naturally occurring carotenoids into retinoids exerted by the saffron extract (23,70). However, another report indicated that the conversion of carotenoids to vitamin A was not a prerequisite procedure for the anticancer activity of saffron (71). Relatively, it was due to the interaction of carotenoids with topoisomerase II, an enzyme involved in multicellular DNA-protein interactions. In addition, a glucoconjugate isolated from the corm and callus of saffron

could cause swelling and local plasma membrane evagination, which might address how cytotoxicity was mediated via extracellular fluid uptake (72).

Another report showed that saffron contains lectins, which suggests that the anticancer activity of saffron is contributed to in part by lectins (72). After treatment with saffron, the level of intracellular sulfhydryl compounds was increased, while the effects of γ-irradiated saffron were also investigated (73). Data showed that saffron possessed significant anticancer effects on human liver cancer cells via the regulation of tumor growth-related factors (56). Recent studies demonstrated that crocin inhibits angiogenesis and colorectal cancer cell metastasis by targeting NF-kB and blocking TNF-α/NF-κB/VEGF pathways (74). Moreover, crocin inhibited NF-κB-mediated inflammation and proliferation in cancer cells through down-regulating protein levels of protein kinase C theta (75). However, to date, the exact anticancer mechanisms of saffron and its main constituents on tumor metabolism are still largely unclear, and further studies are needed.

Host immune responses—The immune system plays a pivotal role in both the progression and prevention of even the most chronic maladies, including cancer. In recent years, some studies have investigated the immunoregulatory effects of saffron and its constituents. The homeostasis between T-helper 1 (Th1) and T-helper 2 (Th2) activity is included in an immune regulation theory. The immunomodulatory activity of a saffron extract was studied on the Th1 and Th2 limbs of the immune system. After oral ingestion of saffron, a significant elevation of CD19 + B cells and IL-4 cytokine was potentiated. However, no significant up-regulation of the Th1 cytokines was observed, including IL-2 and IFN-γ. These results indicate the up-regulation of the Th2 response of saffron is selective and suggest its potential for Th2 immuno-modulation (76). A clinical study of crocin was conducted for stimulating dendritic cells and suggested that crocin can enhance T cell proliferation in leukemia patients (77).

Cancer frequently develops in inflamed tissues, suggesting that carcinogenesis is closely related to inflammation. The antioxidant and anti-inflammatory effects of saffron contribute to its anticancer potential. Many of the carcinogenetic effects of TNFα is mediated by the NF-κB pathway, which has been an important target for cancer chemoprevention and therapeutics. In a liver cancer rat model, saffron showed suppressing effects on NF-kB activation. Both COX-2 and iNOS protein expressions were also inhibited by saffron *in vivo*, while COX-2 and iNOS are key enzymes included in the proinflammatory signals. In addition, administration of saffron significantly down-regulated TNFα receptor activation. These results suggest that anti-inflammatory effects of saffron play a role in its potential for carcinogenesis inhibition (56). Similar effects were observed in crocin. Crocin restored the levels of hepatic MPO (a neutrophil infiltration marker), and subsequently showed strong potential to eliminate rats' inflammation. By the down-regulation of NF-κB, IL-8, COX-2, iNOS and TNF-α, crocin's antitumor activities could be mediated via its anti-inflammatory potential (78).

Future perspectives

Cancer chemotherapy, the chemical intervention in cancer with naturally originated and synthetic drugs, is a commonly used treatment used for fighting against different cancers. Plant-sourced natural products can effectively inhibit the initiation and development of cancer. Saffron has been used as a folk medicine since ancient times to treat several kinds of health disorders, including cancer. Based on the *in vivo* and *in vitro* experimental data presented in this review, saffron and its main ingredients, especially crocin, have promising potential to decrease the risk of carcinogenesis. Several novel compounds have been identified in saffron, including crocusatin H, which shows significant tyrosine inhibitory activity and gives us more opportunities to identify the anticancer compounds from saffron.

Recently, cancer chemopreventive effects of many herbal medicines have been reported. To date, the anticancer effects of saffron and crocin have not yet been evaluated in human clinical trials. It would be interesting to compare the effects of saffron/crocin with those of other botanicals in cancer patients. Further clinical studies have been conducted to investigate the effects of saffron on the quality of life in patients with malignancies. A saffron-based beverage showed significant positive effects on reducing fatigue in patients with breast cancer (79). Data from another recent clinical trial indicated that using crocin during chemotherapy in breast cancer patients ameliorated their anxiety and depression (80). However, before saffron and crocin can be used in the clinical settings, well-designed controlled clinical trials should be conducted, including compound pharmacokinetic analysis and further exploration of their mechanisms of action in cancer management.

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Table 1

The search strategy summary

Items	Specification
Date of search	2022/10/20
Databases and other sources searched	PubMed, SciFinder, Web of Science
Search terms used	"*Crocus sativus*" AND "cancer" "Saffron" AND "cancer" "Crocin" AND "cancer" "*Crocus sativus*" AND "cancer" AND "mechanism" "Saffron" AND "cancer" AND "mechanism" "Crocin" AND "cancer" AND "mechanism" "*Crocus sativus*" AND "cancer" AND "pathway" "Saffron" AND "cancer" AND "pathway" "Crocin" AND "cancer" AND "pathway"
Timeframe	1980–2022
Inclusion and exclusion criteria	Inclusion criteria: Research articles and reviews in English about themes such as *Crocus sativa*/saffron/crocin and cancer/mechanism/pathway Exclusion criteria: Some papers which we considered with low reliability
Selection process	Chong-Zhi Wang conducted the selection, all authors attended a discussion on the literature selection and obtained the consensus
Any additional considerations, if applicable	Some papers were identified by reviewing reference lists of relevant publications if applicable