

Role of Saffron and Its Active Compound Crocin in Cancer Therapy

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Abstract:

Background and objective:

Cancer is a serious global health issue that greatly impact patient life expectancy and quality of life. Natural products from plant, such as saffron which contain crocin, may help prevent or treat various cancers. Saffron, derived from the *crocus sativus* plant, primarily contain crocin. It has been used traditionally as a folk medicine and has shown promise in preventing cancer. This review aims to discuss recent research on how saffron and crocin may help in managing cancer and to explore the mechanism behind their effects.

Methods:

Researchers reviewed English-language publications from January 1980 to September 2022 about the effects of saffron and its component Saffron's bitter taste comes from a compound known as β -D-glucoside. crocin on cancer using databases like PubMed, SciFinder, and Web of Science.

Key content and finding:

This article first explains the chemical studies of this plant. It then discusses how saffron and crocin affect human cancer cells. Saffron and crocin have strong effects in stopping the growth of human cancer cell lines. They are effective against several types, such as colorectal cancer, breast cancer, lung cancer, prostate cancer, cervical cancer, leukemia, glioblastoma, and rhabdomyosarcoma. The text summarizes mechanisms related to cancer treatment, including stopping the cell cycle, causing cell death through caspases, affecting tumor metabolism via signaling pathways, and managing immune system-related inflammation.

Keyword: *Crocus sativus* and saffron, crocin, anticancer, immune response, signaling pathway.

Introduction:

Cancer is a significant health issue worldwide and is a major cause of death in the United States and globally. Treating cancer patients involves surgery, radiation, and chemotherapy, but these cause significant side effects. Studies indicate that cancer patients frequently choose complementary and integrative medicine to treat cancer, alleviate symptoms, and reduce side effects from chemotherapy. Combining natural products or herbal medicines with conventional chemotherapy could improve cancer treatment by restoring body balance and preventing tumor growth and spread. Nature offers a wide range of unique therapeutic substances

due to its immense chemical variety from plants, oceanic elements, and microorganisms.

Natural products have long been a reliable source for medical treatments. More than 65% of medicines used in clinics come from natural sources. Plants and their chemical compounds, including modified versions, play a crucial role in creating new cancer drugs. Herbal medicine has been a key component of chemotherapy treatments for the past 60 years. Several anticancer candidate compounds, including acronyciline, bruceantin, flavopiridol, and thalicarpin, are now being tested in clinical trials. Natural products offer advantages over conventional cancer treatments, such as being less expensive and having fewer or no toxic side

effects. Patients with various cancers are using multiple herbal medications as alternative treatments.

A study on epidemiology data suggests that using herbal medicines for a long time may lead to a significant decrease in the occurrence of cancer types that are not linked to specific organs. Studies using test tubes and animals have shown that ginseng compounds and their metabolites might help prevent cancer. 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).

New high-throughput screening methods allow natural product compounds and their metabolites to provide numerous lead structures for developing effective anticancer agents with fewer side effects. *Crocus sativus*, which is part of the iris family (Iridaceae), is known for its significance and distinctive features.

This plant grows mostly in Mediterranean countries, India, and parts of China, like Tibet. The flower of this plant has chemicals that could be used for medical treatments. It has been used in traditional medicine for a long time. The flower of this plant has chemicals that could be used for medical treatments. It has been used in traditional medicine for a long time.

Saffron has several medicinal properties, including reducing spasms, calming nerves, aiding digestion, stimulating body functions, and promoting menstrual flow. It contains compounds like crocin, crocetin, carotene, and lycopene. Some compounds have various medicinal effects. They can help treat different health issues, including cancer, by stopping cancer cells from .Crocetin and crocetin di-glucose ester can remove harmful free radicals, particularly superoxide anions. This ability helps protect cells from oxidative stress, which is linked to various neurodegenerative disorders. Saffron extract and crocin have shown potential in cancer prevention and treatment through experimental studies. This review aims to highlight the research progress on the anticancer effects of saffron and its active component crocin. It also seeks to explain the

mechanisms through which they act against cancer. Saffron and crocin, used as dietary supplements, are generally recognized as safe due to their long history of use.

Phytochemical and studies on saffron :

Saffron stands out for its distinct properties: a strong red color, a unique aromatic smell, and a bitter taste. Over 150 compounds have been extracted and identified from saffron, as summarized in a recent review article. Saffron's bitter taste comes from a compound known as β -D-glucoside.

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Active benefits against the toxicity caused by cisplatin, a chemotherapy drug. Data indicates that saffron may help prevent. Picrocrocin is a stable

compound found in fresh saffron. However, when heated or stored for a long time, it breaks down into safranal and other volatile aldehydes. In the market, saffron that goes through quality control typically contains about 30% crocin, which contributes to its color. It also has 5% to 15% picrocrocin, providing taste, and up to 2.5% of volatile compounds, including safranal, which gives its aroma. Saffron must have studies using cells and animals shows that saffron, crocin, and related compounds may help prevent cancer.

Cancer cell growth inhibitory effects

Saffron can stop cancer cells from growing while not affecting healthy cells, even in small amounts. Saffron has the ability to inhibit the growth of cancer cells without harming healthy cells, and it is effective even in small quantities. Saffron inhibits cancer cell growth, depending on concentration, without affecting normal cell growth. Saffron has been found to have notably stronger effects on lung cancer cells compared to normal lung fibroblast cells (WI-38) in a study. Crocetin, a compound from saffron, inhibits cell growth in HeLa, A-549, and VA-13 cancer cell lines by regulating DNA/RNA and protein synthesis. Saffron and crocins can help stop the growth of glioblastoma and rhabdomyosarcoma cancer cells.

Pious tumor cells and surgical samples, including ovarian carcinoma, fibrosarcoma, and osteosarcoma. Saffron does not cause genetic mutations and can help prevent mutations induced by benzo[a]pyrene. Saffron can inhibit human cancer cell growth without affecting normal cells. Crocin, found in saffron, greatly reduced the growth of human colorectal cancer cell lines (HCT-116, HT-29, and SW-480) and non-small cell lung cancer cell lines (NSCLC). The extract inhibits the growth of cancer cells but does not affect the normal cells at the concentrations used for testing cancer cells. A study found that saffron and crocetin can attach to the NMDA and sigma-1 receptors at the PCP binding site. Crocins and picrocrocin showed no binding effect, while saffron inhibited growth in human and mouse cells. Saffron reduces cell growth in MCF-7

cells after 48 hours by inducing apoptosis, confirmed with caspase inhibitors.

Specific amounts of crocin, safranal, and picrocrocin when mature. The toxicity data indicates that saffron is considered safe for humans, as experiments on animals show that its lethal dose (LD50) is as high as 20 grams per kilogram.

Saffron and crocin on cancer management

Studies have found promising data showing the effects of saffron on various cancer cells. More evidence froms

Antitumor effects in animal models

In a study using a mouse model for skin tumors, saffron was found to delay the formation of papillomas and reduce their number, showing its potential to inhibit skin tumor initiation and progression. Saffron intake can reduce skin cancer caused by 20-methylcholanthrene in mice. Saffron helped mice live longer when treated with cisplatin and minimized weight loss, white blood cell decrease, and hemoglobin level drop. In a study using rats, a combination of saffron, vitamin E, and cysteine showed protective disease through its detoxification system, ability to modulate lipid peroxidation, and antioxidant properties.

Crocetin, a compound found in saffron, helps reduce bladder toxicity caused by the anticancer agent cyclophosphamide, while maintaining its effectiveness against cancer. In an animal study, saffron combined with cysteine significantly reduced the toxic effects of cisplatin, such as changes in enzyme activity and kidney damage. Evidence indicated that crocin reduced the rate at which cancer was induced in a lung cancer animal model. It achieved this by regulating marker enzymes and increasing serum lipid peroxidation levels. Research using animal models has shown that saffron and crocin may have anticancer effects, particularly against pancreatic cancer and Dalton's lymphoma.

Studies using various animal models have shown that saffron and crocin have anticancer properties, specifically against pancreatic cancer and Dalton's lymphoma. Crocin, a water-soluble carotenoid found in saffron, is a significant active

compound against cancer and is considered the most promising part of saffron extract for this purpose. A study was conducted using rats with colorectal tumors to assess the impacts of long-term treatment with crocin. Treatment with crocin over a long period of time improves the survival rates of rats with colon cancer. This treatment does not cause significant toxic side effects.

Adjuvant cancer therapies

Saffron helps prevent changes in serum enzyme activity, lowers blood glucose, serum creatine, and blood urea nitrogen levels. Pretreatment with saffron water extract can significantly reduce the genotoxic effects caused by cisplatin. It also inhibits the expression of urethane, mitomycin, and cyclophosphamide.

Saffron shows better tumor-killing effects when taken orally. Encapsulating saffron in liposomes can enhance its effectiveness. The text discusses the impact of liposome encapsulation on tumor growth. It highlights that using liposome encapsulation as a treatment effectively slows down the growth of transplanted tumors. The focus is on the significant inhibitory effect observed when this method is applied.

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A study found that saffron, when encapsulated in liposomes, boosted its ability to inhibit solid tumors in mice. Another study also tested saffron's effects on mice, noting its potential benefits. Mice with tumors lived longer when given oral saffron extract treatment. Crocetin has shown promise in treating various cancers. Research indicates it may be a safe and effective treatment for ATRA-sensitive cancers in women.

In cancer treatment, the effectiveness of anti-tumor drugs is limited due to their harmful effects on DNA. Researchers tested if saffron could protect against these effects by giving saffron to mice before they received anti-cancer drugs like mitomycin C, cyclophosphamide, and cisplatin. They found that saffron reduced DNA damage, suggesting it might protect cells by acting as an antioxidant and anti-genotoxic agent. This means saffron could

potentially be used along with chemotherapy treatments.

Mechanisms of saffron for cancer

Chemoprevention

Saffron and crocin exhibit anticancer effects through various mechanisms. They influence cell cycle progression, induce apoptosis, regulate tumor metabolism, and modulate immune responses.

Cell cycle arrest

The cell cycle is a series of events that result in cell division, encompassing phases such as G1, S, G2, and M, with the process being crucial for cell reproduction. Cancer cells lose normal growth control, leading to unchecked proliferation and the ability to sustain growth signals. Controlling these processes is essential to mitigate cancer spread. Saffron has been studied for its potential to induce cell cycle arrest as an anticancer mechanism. In studies involving liver cancer and other forms, saffron was shown to increase cell cycle arrest, specifically in a metastasis-associated gene (MACC1)-dependent manner. Saffron inhibited colon cancer proliferation, with more significant effects observed in cells expressing higher levels of MACC1, indicating its targeted influence. Crocin, a component of saffron, has demonstrated tumor growth inhibition in various cancers.

It has shown anti-leukemic effects by inducing cell cycle arrest in human leukemia cells in both concentration and time-dependent manners. Crocin also affects cell cycle progression by down-regulating cyclin D1 and altering cell cycle phases like G0/G1, suggesting it may suppress cancer via a p53-dependent pathway. These findings highlight saffron and crocin's potential roles in cancer treatment through cell cycle modulation.

Induction of cell apoptosis

Apoptosis is a type of programmed cell death that helps remove unwanted or defective cells. Many cancer treatments, like chemotherapy, natural compounds, radiation, immunotherapy, and cytokines, work by triggering apoptosis in cancer cells. Saffron has shown effects on cancer cells

related to the p53 protein, which is involved in apoptosis. In studies, saffron was found to inhibit the growth of colon cancer cells by causing apoptosis, confirmed by DNA damage tests. In tumor cells with high levels of p53, saffron induced cell death through over-activation of a protein called BAX, indicating that p53 might be important for saffron's ability to cause cancer cell death through apoptosis.

In the 1990s, studies using HeLa cell models showed that crocin caused changes in cell shape, such as shrinking and piknotic nuclei, indicating its potential to inhibit cancer cell growth.

Crocin has been studied for its ability to trigger cell death in different types of cancer cells. In prostate cancer cells, crocin induces apoptosis mainly through the intrinsic pathway by activating caspase-9. In gastric adenocarcinoma cells, crocin triggers apoptosis by activating caspases and altering the Bax/Bcl-2 ratio. In breast cancer cells, crocin inhibits cell growth by causing apoptosis, involving caspase-3 pathways and extensive DNA damage. Apoptosis in cancer cells can occur through intrinsic or extrinsic pathways, involving caspase activations. Studies show that crocin involves both pathways, indicated by the activation of caspases 8 and 9, suggesting dual pathway involvement in inducing apoptosis.

Tumor metabolism regulation

Early theories about saffron's anticancer abilities included its effects on cell metabolism, namely DNA and RNA synthesis, the inhibition of free radical chain reactions, and the conversion of carotenoids into retinoids. However, research suggested that carotenoid conversion to vitamin A wasn't necessary for saffron's anticancer actions. Instead, carotenoids' interaction with the enzyme topoisomerase II was important. A glucoconjugate from saffron also played a role by affecting cell membranes and fluid uptake, indicating another potential anticancer mechanism.

Saffron contains lectins, which might help its anticancer properties. It raises intracellular sulfhydryl levels, and its anticancer effects on human liver cancer cells are noted. Crocin in saffron inhibits angiogenesis and cancer metastasis by targeting

specific pathways. It also reduces inflammation and cancer cell growth. However, the precise mechanisms by which saffron fights cancer remain unclear, and more research is needed to understand its impact on tumor metabolism.

Host immune responses

The immune system is crucial in managing diseases, such as cancer. Recent studies have explored saffron's effects on immune regulation. Research shows that saffron extract increases Th2 response by elevating CD19 B cells and IL-4 cytokine, without significantly affecting Th1 cytokines. This suggests saffron supports Th2 immuno-modulation. Additionally, crocin was studied for stimulating dendritic cells, showing potential to enhance T cell growth in leukemia patients.

Cancer often starts in inflamed tissues, indicating a link between cancer development and inflammation. Saffron has antioxidant and anti-inflammatory properties that are useful in fighting cancer. It was found to suppress NF- κ B activation, COX-2, and iNOS protein expressions, which are involved in inflammatory processes. Additionally, saffron reduced the activation of the TNF α receptor, a protein involved in inflammation. These findings suggest saffron's potential in inhibiting cancer development through its anti-inflammatory properties. Crocin, a component of saffron, also shows similar effects by restoring hepatic MPO levels, a marker for neutrophil infiltration. Crocin has shown strong potential for reducing inflammation in rats. It could mediate antitumor activities by decreasing NF- κ B, IL-8, COX-2, iNOS, and TNF- α , indicating its anti-inflammatory properties.

Future perspectives

Chemotherapy uses chemicals, both natural and synthetic, to treat cancer. Plant-based products can help prevent cancer growth. Saffron, a traditional remedy, shows promise in cancer treatment, particularly due to its ingredient crocin. Saffron compounds like crocusin H demonstrate potential anticancer properties, offering new treatment opportunities.

Recent exploration has stressed the cancer-preventative goods of colorful herbal drugs, although saffron and crocin have n't been completely explored in mortal trials for their anticancer parcels. It's important to compare saffron and crocin with other herbal remedies in cancer cases. Some studies have delved saffron's impact on quality of life in cancer victims, with one saffron- grounded drink perfecting fatigue in bone cancer cases. Another study showed crocin reduced anxiety and depression during chemotherapy. Yet, more detailed clinical trials are demanded to examine saffron and crocin's pharmacokinetics and mechanisms of action in cancer treatment.

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Conclusion:

Studies show saffron and crocin can improve life quality in cancer patients, making them promise for future cancer studies.

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