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Saffron and cancers: A systematic review

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Abstract

Background: Saffron is a spice known for its preventive and curative properties.

Objectives: This research aims to review the toxicity of saffron extract and its constituents on both normal and cancer cells, providing valuable insights into its potential therapeutic applications.

Methods: A systematic search of studies was conducted using databases such as PubMed, ScienceDirect, and SID to gather relevant literature on the subject.

Results: Saffron demonstrates selective toxicity towards cancer cells through various mechanisms, including the inhibition of RNA and DNA synthesis, as well as the promotion of apoptosis. Among its constituents, crocin emerges as a significant anticancer agent within saffron, attributed to its ability to modulate gene expression and induce apoptosis in cancer cells. Additionally, crocetin has been found to inhibit the growth of cancer cells by disrupting DNA, RNA, and protein synthesis in neoplastic cells, inhibiting RNA polymerase II, and interacting with histone H1 and H1-DNA structures. Animal studies have also shown that saffron, crocin, and crocetin possess anticancer and cancer-preventive properties.

Conclusions: This study concludes that saffron extract, along with its constituents crocin and crocetin, exhibit selective toxicity against cancer cells and demonstrate cancer preventive effects. Importantly, the toxicity of saffron and its constituents towards normal cells is minimal, with even oral administration showing low toxicity levels.

Keywords: Saffron, Cancer, Review.

Introduction

Cancer is the leading cause of death globally, with over 8 million new cases diagnosed each year. In 2010, approximately 1,530,000 new cancer cases and 570,000 cancer-related deaths was reported in USA.[1] Different types of cancer exhibit varying prevalence rates across populations, influenced by factors such as immigration and genetic predisposition.[2] Studies suggest that lifestyle choices and environmental factors, including dietary habits, play a crucial role in cancer prevention.[3,4] Recently, there has been growing interest in chemoprevention strategies using botanical ingredients and spices to inhibit tumor growth and cancer progression.[5]

Saffron, Crocus sativus L. plant, is renowned as the most expensive spice globally and has a rich history of traditional use. The dried stigma of saffron has been utilized as a spice for centuries,[6-12] with an estimated annual global production of 300 tons, primarily originating from Iran.[13,14] Historically, saffron has been employed in Iranian traditional medicine for various purposes, including alleviating stomach pains, acting as an antispasmodic, aiding digestion, relieving renal colic pains, combating depression, and enhancing appetite.[15]

The therapeutic properties of saffron stem from its key metabolites, such as crocin, picrocrocin, and safranal. Crocin is responsible for the red color of saffron, picrocrocin contributes to its bitter taste and safranal imparts its unique aroma. Picrocrocin accounts for 1 to 13% of dry saffron weight and is the primary source of

saffron's bitterness. Saffron also contains carotenoids like crocetin and glycosidic forms of crocetin (Crocin), along with lycopene, alpha-carotene, beta-carotene, and zeaxanthin. Additionally, flavonoids, amino acids, proteins, starch, resins, and trace amounts of vitamins like thiamine and riboflavin have been identified in saffron.[16-25]

Previous studies have demonstrated the antioxidant and anti-inflammatory properties of saffron extract and its active constituents, leading to its potential therapeutic benefits.[26,27] While research has explored the effects of saffron in cancer prevention and treatment, the exact mechanisms underlying these effects remain to be fully elucidated.

An herb used as a chemopreventive agent should ideally be non-toxic or have minimal toxicity, demonstrate high efficacy, be orally administrable, have well-understood mechanisms of action, and be cost-effective.[5] In this review, we aim to comprehensively examine the anticancer effects of saffron and its constituents, as well as the proposed mechanisms of action. Furthermore, we will explore studies on the toxicity of saffron and its constituents to assess the safety profile of saffron as a chemopreventive herb.

Methods

This study is a review article sourced from PubMed and ScienceDirect. Keywords such as saffron, crocin, crocetin, safranal, colchicum, cytotoxicity, toxicity, cancer, neoplasm, tumor, tumoricidal effect, and detrimental effect were utilized. SID as a national database was also consulted to access relevant studies. Interventional studies involving human populations, in vitro and in vivo animal studies from 1975 to 2014 were included in the review. However, no human studies associating saffron with cancer were found in our search.

Results

In vitro Studies

Saffron

An in vitro study assessing the impact of saffron extract on macromolecule synthesis in cell layers, including cells from lung tumors, normal lung fibroblasts, and virus-transformed fibroblast cells, revealed that malignant cells are more susceptible to saffron's inhibitory effects on RNA and DNA synthesis compared to healthy cells.[28] This inhibition is a key mechanism underlying saffron's anti-tumor and anti-carcinogenic effects.[17,28-31] Another study investigated the effects of saffron extract at various doses (200 to 2000 mcg/ml) on Hela and Hep G2 cells over 24, 48, and 72 hours. The IC50 values against these cells were 800 and 950 mcg/ml after 48 hours. While apoptosis played a significant role in the toxic effect, other mechanisms besides apoptosis may contribute to these effects. The study observed substantial inhibition of colony formation and DNA/RNA synthesis (50% inhibition) at concentrations of 100 to 150 mcg/ml, with protein synthesis inhibition even at higher concentrations.[32] Various mechanisms, such as free radical chain reactions, interference with nucleic acids, carotenoids affecting topoisomerase II expression, and potential synergistic effects of saffron phytochemicals, contribute to its anticancer properties.[17,26,33] Afshar et al. reported that saffron extract exhibited cytotoxic effects against Hep G2 and human cervical carcinoma cells but not against normal rat fibroblast cells.[34] In another study on human alveolar adenocarcinoma cells (A549), different concentrations of saffron extract (100, 200, 400, and 800 mcg/ml) were tested over three days. The results indicated a dose-dependent increase in apoptotic cells in the presence of saffron, with researchers observing caspase-dependent apoptosis pathways activation. Control cells (human lung fibroblasts) were less affected by the extract. The study suggested that saffron's anti-tumor action involves inhibiting cell proliferation and stimulating apoptosis through caspase-dependent pathways.[35] Additionally, the study indicated that saffron extract up to 1500 mcg/ml levels is non-toxic, non-mutagenic, and does not exhibit anti-mutagenic properties.[36] In vitro studies have shown that saffron can stimulate cell mitogenesis in lymphocytes in a non-specific manner, suggesting a potential immunological mechanism for its anti-tumor activity. However, the combination of Saffron Cottage (Jnsnvzyd and cannabinoid) did not reverse multidrug resistance in lymphoma cells.[29,37] Other studies have isolated bioactive substances from the saffron plant.[38,39] The IC50 against HeLa cells was found to be 9 µg/ml. The toxicity of this substance was assessed on human malignant cell layers, non-malignant cell layers, blood cells, and hair follicles in culture. The IC50 values for tumor cells ranged from 7 to 22 µg/ml, while it was 100 µg/ml for normal fibroblasts. This indicates an eight-fold higher toxicity in tumor cells compared to non-tumor cells.[32]

In conclusion, saffron has been shown to inhibit mechanisms of RNA and DNA synthesis and induce apoptosis, displaying selective toxicity against cancer cells.

Crocin

The researchers examined the combined effects of four major compounds found in Spanish saffron, namely crocin, crocetin, picrocrocin, and safranal, on cervical carcinoma HeLa cells. Among these compounds, Crocin exhibited the most significant effect. The inhibitory effect of saffron extract on the growth of HeLa cells in vitro (ID50 = 2.3mg/ml) and the inhibition of apoptosis were primarily attributed to crocin (ID50 = 3μM). In contrast, picrocrocin and crocetin showed lower effects with ID50 values of 3mM and 8/0, respectively. The toxicological effects of crocetin were not observed in this study.[40]

Crocin is considered an important anti-cancer compound present in saffron. Another study indicated that crocin and dimethyl crocetin from saffron are not mutagenic.[41] Molnar et al., reported that crocin and crocetin exhibit inhibitory effects on Glucosyltransferase at different doses, affecting the initial expression of tumor antigens in adenovirus-infected cells.[37] The presence of sugars appears to influence the toxicity of crocin and crocetin, as high doses did not cause inhibition of cell growth.[42]

Garc-Olmo et al., reported that crocin exhibits potent cytotoxic effects against HT-29 cells and DHD/k12 (adenocarcinoma cells in rat and human colon adenocarcinoma cells), with LD50 values of 4.0 mM1. Crocin induces the formation of large cytoplasmic vacuole-like regions and significant decreases in cell cytoplasm.[43] Microscopic studies have shown that treatment of HeLa cells with crocin leads to vacuolization areas, reduction in cell nucleus size (Pyknosis), indicating programmed cell death stimulated by crocin.[42,43]

Research has also investigated the impact of crocin on Hep G2 cells, revealing toxicological effects at a concentration of 3 mg/ml after 48 hours. Crocin treatment resulted in a 51% decrease in telomerase activity and a 60% reduction in the relative gene expression of telomerase catalytic subunit, showing dose-dependent effects. Given that cancer cells exhibit higher telomerase gene transcription compared to normal cells, the selective effects of crocin on cancer cells are apparent.[44]

Furthermore, a study demonstrated that crocin derived from saffron significantly inhibited the growth of three layers of colorectal cancer cells (HCT-116, SW-480, and HT-29) in a dose-dependent manner, highlighting its potential for cancer treatment.[45] The neuroprotective effect of crocin, at doses of 10, 20, and 50 micromoles, has been linked to its antioxidant properties and dose-dependent cytotoxicity against acrylamide-induced PC12 cells.[46] Other mechanisms of action include inhibition of protein aggregation and fibril formation.[47]

Overall, crocin derived from saffron is recognized as a potent anti-cancer compound. Its effects are believed to be mediated through gene alterations and the induction of apoptosis in cancer cells.

Crocetin

Crocetin has been the subject of several studies investigating its anticancer properties. While some studies have not included crocetin from saffron as a significant factor,[40,42] others have highlighted its importance.[45, 48-55] For instance, a study examined the inhibitory effects of crocetin from saffron on intracellular protein and nucleic acid synthesis in various human malignant cell lines, including HeLa cells, lung adenocarcinoma cells, and transformed fetal lung fibroblasts. The results showed a dose-dependent inhibition of protein and nucleic acid synthesis by crocetin, although it did not affect colony formation.[31] Additionally, other studies have shown that dimethyl crocetin and crocin inhibit the growth of cancer cells at 8/0 and M μ 2 doses for 50% inhibition (ID50).[30,42]

Toxicity studies of dimethyl crocetin and crocin in various cell layers (DLA, EAC, S-180, leukemia L1210, and leukemia P388) and human primary cells from surgical specimens (osteosarcoma, fibrosarcoma, and ovarian carcinoma) have been conducted. These studies have demonstrated significant inhibition of nucleic acid synthesis and have suggested that dimethyl crocetin can disrupt DNA-protein interactions, such as topoisomerase II, which are crucial for cellular DNA synthesis.[29,48] Additionally, toxic effects of crocetin against non-solid tumor cell layers and various layers of human tumor cells and primary cells derived from surgical specimens have been observed.[30,49]

In another study, the cytotoxic effects of crocetin at doses of 5-20μg/ml were compared with Plantyn cis-selective effects against human rhabdomyosarcoma cells, showing less impact on normal cells.[50]

The effects of crocetin on specific types of cancer include:

1) Breast Cancer: Chryssanthi et al., observed that crocetin and its analogs inhibit the proliferation of breast cancer cells. In their study, crocetin demonstrated a dose-dependent inhibition of MDA-MB-231 and MCF breast cancer cell proliferation independent of the estrogen receptor.[51]

2) Cervical Cancer: Saffron crocetin-like compounds at doses of 1-200μg/ml significantly reduced colony formation in Hela cells and inhibited RNA and DNA synthesis. Crocetin also inhibits DNA-dependent RNA polymerase II enzyme and RNA synthesis, suggesting a

molecular-level interaction with tRNA.[34,53]

3) Leukemia: Studies have shown that crocetin exhibits cytotoxic effects against promyelocytic leukemia cells (HL60) and human myelogenous leukemia cells (K562) at lower doses, as well as in other leukemia cell layers (L1210 and P388).[30,42]

4) Liver Cancer: Crocetin treatment in fibroblasts activated with aflatoxin B1 (AFB1) significantly inhibited cytotoxicity and DNA-adduct formation. This protective effect is attributed to increased cytosolic glutathione (GSH) levels, leading to the activation of glutathione-S-transferase (GST) formation. Crocetin also inhibits the formation of malondialdehyde (MDA) induced by reactive oxygen species (ROS), providing protection against oxidative damage.[54, 56, 57]

5) Lung Cancer: Crocetin inhibited nucleic acid synthesis and colony formation in lung carcinoma cells A549 and SV-40 transformed fetal lung fibroblasts VA13.[32]

6) Pancreatic Cancer: Studies have demonstrated the anti-cancer potential of crocetin on pancreatic cancer cells, inhibiting cell proliferation in various cell lines and in Xenograft athymic rat models. Crocetin also inhibits DNA synthesis in pancreatic cancer cells and may affect the balance between anti-apoptotic proteins (Bcl-2) and pro-apoptotic proteins (Bax) to exert anti-tumor effects [58]. Additionally, low-dose paclitaxel combined with crocetin has shown promise in inhibiting pancreatic cancer cell proliferation and inducing apoptosis, potentially enhancing the efficacy of conventional chemotherapy drugs.[59]

Overall, crocetin inhibits cancer cell growth by reducing DNA, RNA, and protein synthesis, as well as interfering with RNA polymerase II activity in neoplastic cells.[31] Additionally, crocetin may interact with histone H1 structure and H1-DNA, suggesting potential epigenetic mechanisms underlying its anticancer effects.[60]

In vitro studies – on animals

Saffron

In vitro studies on animals have shown promising results for saffron in cancer regulation. Salomi et al., conducted a 12-week trial to examine the effects of saffron extract on cancer induced in albino rats. The study revealed that while 90% of the control group had HPV (HPV 2 to 7), the group treated with saffron at a dose of 26/0 mg/kg had only one papilloma. High doses of the saffron extract inhibited and delayed the initiation and progression of skin tumors in rats, as well as reduced tumor incidence in soft tissue sarcoma.[48] These effects were attributed to the regulation of lipid peroxidation by the extract, which is rich in carotenoids, antioxidants, and detoxification systems.[41,48]

A study has shown the effects of a lipid peroxidation-regulating extract rich in carotenoids, antioxidants, and detoxification systems on cancer cells.[61] Previous research has indicated that the antitumor effects of saffron are more effective through liposome encapsulation compared to intravenous or oral administration. Encapsulation in liposomes significantly inhibited the growth of tumor cells implanted in rats.[62] Oral treatment with an alcoholic extract of Crocus sativus (200 mg/kg) in male albino rats with sarcoma cells implanted into their sternum increased their lifespan.[29,63] Similarly, oral treatment with the extract in mice led to elevated levels of β-carotene and vitamin A,[64] suggesting that the performance of saffron's carotenoids, vitamin A, and anti-cancer effects are interdependent. This is supported by studies showing that β-carotene, a precursor of vitamin A, has anticancer properties.[30]

In a study investigating the effects of an aqueous extract of saffron on gastric cancer induced in rats, it was found that saffron (at doses of 100-175 mg/kg) inhibited cancer progression in a dose-dependent manner. Rats treated with higher doses of the extract showed complete normalization in 20% of cases by the end of the study, with no adenoma formation observed. Saffron introduced a mechanism involving increased apoptosis and decreased proliferation as a means of verifying its efficacy. Furthermore, the serum enzymes and antioxidants returned to normal levels after cancer induction in the saffron-treated group.[65] Despite the positive findings regarding saffron's benefits, further in vivo studies on the components of saffron crocus are warranted due to limited research in this area.[33]

On the other hand, studies have shown that rats treated with cisplatin extract experience increased longevity and reduced drug-related side effects.[66-68] Pre-treatment with saffron (at doses of 20, 40, and 80 mg/kg) significantly reduced the toxicity of anticancer drugs in Swiss albino mice.[69] Additionally, animals treated with cysteine (20 mg/kg) and saffron extract (50 mg/kg) experienced a significant reduction in the toxic effects caused by cisplatin.[64] These findings suggest that saffron may mitigate the toxic effects of cancer drugs through an unknown mechanism.

Crocin

A study was conducted to investigate the effects of long-term treatment with crocin (400 mg/kg) on tumor growth and the longevity of rats with tumors induced by

subcutaneous injection of colorectal adenocarcinoma cells. The results showed that crocin treatment significantly increased the survival of the animals, with particularly high tumor growth observed in females. This suggests that the efficacy of crocin in female subjects may be influenced by hormonal factors.[43] Another study indicated that crocin reduced cytotoxicity in rat blood without completely inhibiting it.[70]

Crocetin

In frog embryos, crocetin from saffron has shown effectiveness in treating certain types of cancer when used in conjunction with all-trans retinoic acid (ATRA). It has been proposed that crocetin could be a safer alternative for treating cancers in women of childbearing age who are susceptible to ATRA.[49] Research by Dhar et al., demonstrated that crocetin exhibits anti-tumor properties both in vitro and in vivo, particularly in pancreatic cancer. Female hormones may also play a role in enhancing this effect.[58]

Studies have shown that pre-treatment with crocetin (2 to 6 mg/kg) in rats protects the liver from damage caused by AFB1 by increasing liver GSH levels and activating GST and glutathione peroxidase (GSH-Px), which reduces AFB1-DNA adduct formation.[55] Additionally, crocetin significantly suppressed AFB1-induced hepatotoxic lesions in rats by reducing the activity of enzymes such as AST, ALT, alkaline phosphatase, and GGT after pretreatment with crocetin.[72]

In vivo studies have demonstrated that crocetin (20 mg/kg) exhibits anti-tumor activity in animal models of lung cancer by enhancing the activity of enzymes involved in metabolizing free radicals from drugs. Crocetin inhibits lipid peroxidation and increases the activities of GST, GSH-Px, catalase, and Superoxide Dismutase. Furthermore, crocetin reduces marker enzyme levels associated with carcinogenic benzo(α)pyrene ingestion in lung tissue.[73]

Research by Magesh et al., revealed that crocetin (50 mg/kg) inhibits the proliferation of lung cancer cells and may protect against pulmonary carcinogenesis induced by benzo(α)pyrene in Swiss albino mice. In animal models of pancreatic cancer, crocetin (40 mg/kg) inhibited tumor proliferation by targeting EGFR phosphorylation and expression.[74]

Moreover, crocetin (600 mg/kg) has been shown to delay the onset and formation of skin tumors induced by DMBA and castor oil in rats. Additionally, crocetin exhibited antitumor activity in rats with DMBA-induced skin cancer and castor oil hair.[75,76]

In summary, crocetin demonstrates anti-cancer and cancer-preventive effects, potentially through regulating antioxidant enzymes in the body.

Saffron Toxicity

The evidence regarding the toxicity of saffron indicates that it is relatively low.[17,29,63,77,78] Animal studies have determined oral LD50 of saffron to be between 7 to 20 grams per kilogram.[17] However, there are conflicting results from studies on the harmful effects of saffron.[15] Some studies suggest that injection of 2.1 grams per ABW may lead to symptoms such as nausea, vomiting, diarrhea, and bleeding, while other studies have reported toxicity even with daily doses exceeding 4 grams over several days, including in pregnant women. High doses of saffron, more than 10 grams, have been associated with side effects such as decreased appetite, insomnia, nausea, vomiting, and dizziness.[15] In rare cases, consuming too little saffron may lead to allergies.[79]

The ID50 set for saffron in one study is 20 grams per kilogram, indicating that researchers consider saffron safe for human consumption.[77] In vivo animal studies have shown that the toxicity of saffron and its components is very low or even zero.[29,63,78] For example, in a study on the toxicity of Safranal, intraperitoneal LD50 values were determined for male mice (48 ml per kilogram), female rats (88 ml per kilogram), and male rats (50 ml per kilogram). Oral LD50 values were also determined for male mice (42 ml per kilogram), female rats (42 ml per kilogram), and male rats (53 ml per kilogram). The results indicated low toxicity of Safranal through intraperitoneal injections and practically non-toxicity orally.[80]

In a separate study, oral and intraperitoneal doses of crocin (3 grams per kilogram) did not result in deaths in mice within two days.[81] High doses of saffron pills (200 to 400 milligrams per day) have been shown to induce changes in biochemical and hematological parameters in healthy adults, but these changes remained within normal ranges and were not considered clinically significant. Additionally, pharmacologic doses of crocin did not cause deaths or injuries to major organs in the body.[81,82]

It is advised that pregnant women avoid using saffron for medical purposes due to its potential to induce uterine contractions. Overall, the high LD50 values of saffron and its components suggest that toxicity against non-cancerous cells in the body is relatively low.

Conclusions

In conclusion, saffron and its constituents have shown promising anti-cancer effects with selective toxicity

towards tumors. Additionally, saffron and its components have demonstrated potential in inhibiting the toxicity of anti-cancer drugs. While the exact anti-cancer mechanisms of saffron and its components are not fully understood, several mechanisms have been proposed. For instance, saffron may directly target DNA and regulate gene expression. Research by Bathaie suggests that saffron carotenoids, such as crocin, crocetin, and crocetin dimethyl, bind directly to the DNA minor groove, inducing changes in the DNA structure. Moreover, saffron has been shown to induce apoptosis in tumor cells, playing a crucial role in cell death in various cancer cell lines.[65,34]

The anticancer effects of saffron crocetin may be attributed to its ability to inhibit the synthesis of DNA, RNA, and proteins. Crocetin has also been found to inhibit RNA polymerase II in neoplastic cells and interact with histone H1-DNA structure. These findings suggest that the epigenetic mechanisms of crocetin's anticancer effects are diverse and warrant further investigation.

Furthermore, the antioxidant and anti-inflammatory properties of saffron and its components are noteworthy. The impact of saffron on gene regulation and enzyme activity presents new avenues for research. However, clinical trials evaluating the anticancer effects of saffron remain limited, necessitating further studies to determine the effective dose and mechanism of action.

An intriguing aspect of saffron's toxicity is its apparent selectivity towards cancer cells while sparing normal cells. With a reported LD50 classification indicating low toxicity levels, saffron and its components are considered relatively safe for consumption. Despite the lower amounts typically used in daily food intake compared to research studies, the potential benefits of saffron remain significant.[83,84]

In summary, saffron and its components exhibit selective toxicity against cancer cells while preserving normal cell function. However, human studies on the use of saffron in this context are limited, highlighting the need for future research to explore its full potential in cancer prevention and treatment.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

Aflatoxin B1: AFB1; All-trans retinoic acid: ATRA; Glutathione: GSH; Glutathione S-transferase: GST; Malondialdehyde: MDA; Reactive oxygen species: ROS; Glutathione peroxidase: GSH-Px;

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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Availability of data and materials

The data used in this study are available from the corresponding author on request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. Institutional Review Board approval was obtained.

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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