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PROSPECTS

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The antileukemic effects of saffron (*Crocus sativus* L.) and its related molecular targets: A mini review

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Abstract

Saffron (*Crocus sativus* L.), and its main constituents, crocin, and crocetin have shown promising effects as an antileukemic agent in animal models and cell culture systems. Saffron retards the growth of cancer cells via inhibiting nucleic acid synthesis and enhancing antioxidative system. It can induce apoptosis and chemosensitivity via inhibiting multidrug resistance proteins. Saffron also induces differentiation pathways via inhibiting promyelocytic leukemia/retinoic acid receptor-α, histone deacetylase1, and tyrosyl DNA phosphodiesterase-1 as well. The present review highlights the most recent findings on the antileukemic effects of saffron and its underlying molecular targets. The emerging evidence suggests that saffron has a selective toxicity effect against leukemic cells while is safe for the normal cells.

KEYWORDS

antileukemic effects, crocetin, crocin, *Crocus sativus* L., saffron

1 | INTRODUCTION

According to the World Health Organization reports, the prevalence of cancer will increase from 14 million in 2012 to 22 million within the next 20 years. In 2017, it is estimated that there are 62 130 new cases of leukemia and 24 500 deaths because of this cancer in the United States.[1] Leukemia obtained the seventh place out of the 10 most frequent cancer types in male European.[2] In Iran, leukemia is one of the five most common cancers in men, based on the National Cancer Registry reports.[3,4] Leukemia results from hematopoietic stem cells which elude normal control mechanisms and arrest differentiation into mature blood cells. The uncontrolled proliferation of hematological cells results in the accumulation of the malignant cells in bone marrow that affects the physiology of the blood cells.[5]

Despite prognosis improvements of the majority of the leukemic patients, relapse and resistance to new chemotherapeutic agents are still treatment issues. Therefore, the search for novel anticancer drugs with better efficacy and less adverse effects remains important. Dietary phytochemicals are growing interest as an alternative approach for developing anticancer drugs. They have been proven to be safe and display strong antioxidant properties.[6,7] Several phytochemicals have been found to show anticancer activity via decreasing cell proliferation, inducing apoptosis, inhibiting angiogenesis, and preventing metastasis.[8,9] Some of the plant-derived compounds such as Vinca alkaloids, taxol, podophyllotoxin analogs, and carotenoids are now used in cancer chemotherapy.[10,11] There is increasing evidence that *Crocus sativus* L. (saffron) exerts anticancer effects in certain types of

cancer such as leukemia. The present review addresses the most recent findings on the antileukemic effects of saffron and underlying molecular targets.

2 | SAFFRON: IN CANCER CHEMOPREVENTION

Saffron is a yellow-red pigment that is obtained from dry stigmas of the *Crocus sativus* L. flower. It belongs to the Iridaceae family and is principally native to Iran. The saffron crocus is a small, stemless perennial plant with an overall length up to 30 cm and its flower has been seen in the autumn. The chemical constituents of *Crocus sativus* include the carotenoids, crocin (CRC) and crocetin, picrocrocin, safranal (SFR), and the monoterpene aldehydes. Saffron is widely used as a natural dietary spice as well as a popular component in the traditional medicine. Several studies have described the anticancer activity, cytotoxic effects, and antidepressant activity of this plant.[12] Modaghegh et al studied the safety and tolerability of saffron stigma tablets in healthy adult volunteers. Their study was a double-blind and placebo-controlled research which subjects were received 200 and 400 mg doses of saffron for 1 week. Popular health measurements including hematological, biochemical, hormonal, and urine parameters were controlled before and after their experiment. They have reported mild leukopenia, a decrease in amylase, and normal ranges partial thrombin time (PTT).[13] The other study showed very rare allergenic risk for saffron.[14]

Antidepressant property of saffron is well known and approved. Several randomized controlled trials have suggested the efficacy and safety of saffron in patients with mild to moderate depressive symptoms.[15] Depressive symptoms are common psychiatric complications that occur in most individuals with cancer.[16] In addition to antidepressant activities, researchers have shown that saffron has an important therapeutic effect on cancer due to several mechanisms such as proapoptotic,[17] antiproliferative[18] and radioprotective effects.[19] Antimutagenic and comutagenic effects of saffron extract (SE) were explored using the Ames/Salmonella test systems against two well-known mutagen agents (B[a]P and 2AA). SE was shown to inhibit the mutagenesis during in vitro colony formation assay, as well as four different cell cultures including human normal (CCD-18Lu) cells and malignant (HeLa, A-204, and HepG2) cell lines. SE showed no mutagenic activity against (B[a]P)-induced mutagenicity, applying the TA98 strain in the Ames/Salmonella test system. Furthermore, SE demonstrated a dose-dependent comutagenic effect on 2AA-induced mutagenicity. In the in vitro colony formation test system, SE displayed a dose-dependent inhibitory effect only against human malignant cells. Overall, these results suggest that SE might be used as a potential cancer chemopreventive agent.[20-22]

3 | SEARCH STRATEGY

A systematic literature search was performed in Scopus (http://www.scopus.com) and Medline (http://www.ncbi.nlm.nih.gov/pubmed), to identify all published articles dealing with saffron in leukemic cells, without any language restriction. The search terms included ["saffron extract" or "Crocetin" or "Crocin" or "safranal" and "leukemia"] in titles and abstracts. The search was performed up to December 2017.

4 | ANTILEUKEMIC ACTIVITY OF SAFFRON

There are many reports on the effects of SE and its main constituents, CRC, and crocetin on leukemic cells. Table 1 summarizes the antileukemic effects of saffron along with the underlying mechanisms of action.

4.1 | The antileukemic effect of crocetin

Crocetin ($C_{20}H_{24}O_4$; molecular weight, 328.4 g/mol; PubChem CID, 5281232) is one of the main components of saffron and belongs to the large family of natural dyes known as carotenoids. Crocetin crystals with a melting point of 285°C are highly soluble in organic basic solutions such as pyridine. It has been demonstrated that crocetin has antileukemic effects in cell cultures. The chemical structure of crocetin [36] is presented in Figure 1.

Tarantilis et al investigated the effect of crocetin (0.1 to 10 μM) on cell proliferation and differentiation of promyelocytic leukemia (PML) HL60 cells during 3 and 5 days. They compared the effects of crocetin and all-trans retinoic acid (ATRA) solutions using methyl thiazolyl tetrazolium (MTT) and nitroblue tetrazolium (NBT) assays, respectively. At the 5 μM concentration of these solutions, differentiation was induced in 50% of crocetin-treated and 85% of ATRA-treated cells during 5 days. The toxicity of ATRA remains an important limitation for its use at high therapeutical doses. Unlike ATRA, crocetin is not a provitamin-A precursor. Therefore, it could be potentially useful for the patients requiring differentiation therapy the acute PML cases.[23] Moreover, the cytotoxicity of crocetin on other leukemic cell lines (K562, L1210, and P388) have been reported.[24]

TABLE 1 The antileukemic effects of Saffron (*Crocus sativus* L.) in vitro (leukemic cells) and in vivo (animal studies)

Cell lines or animal	SE type	IC_{50}	Mechanism of action	References
HL60, K562, L1210, and P388 cell lines	Crocin and dimethylcrocetine	2 μM against 0.12 μM in ATRA after 5 d	Induction of cytotoxicity and inhibition of cell proliferation	Tarantilis et al,[23] Morjani et al[24]
HL60, NB4, and primary APL cells	Crocetin	EC50 of crocetin: 2.70, 3.30, and 7.0 μM in primary APL, NB4, and HL60 cells, respectively.	Increase apoptosis, inhibition TDP1, MDR, PML-RAR, and HDAC1	Moradzadeh et al,[25,26]
Lymphocytic cells and animal models	Crocetin	LD_{50}, 600 mg/kg IC_{50}: 7-30 μg/mL	Reduction of immunological reaction	Nair et al[27]
K562 and HL60 cell lines	Dimethyl-crocetin and crocetin	7-30 and 11-39 mg/mL for dimethyl-crocetin and crocin in HL60 cells, respectively	Induction of apoptosis in HL60 cells but did not effect on K562 cells	Beljebbar et al[28]
HL60 and primary cells	Crocin	5 and 1.25 mg/mL for HL60 and primary cells during 5 d, respectively	Induction of apoptosis and promote the maturation of dendritic cells	Xu et al,[29,30] Zhang et al[31]
MOLT-4 cell line	Crocin	500 μM for 48 h	Inhibition of cell proliferation, induction of apoptosis, and ROS	Rezaee et al[32]
HL60 and Jurkat cell lines and animal xenograft models	Crocin	0.625-5 mg/mL for in vitro, 6.25 and 25 mg/kg for in vivo	Inhibition of cell proliferation and induction of apoptosis	Sun et al[33,34]
K562 cell line	Crocin and safranal	241 μM for safranal and 160 μM for crocin	Induce cytotoxic response	Geromichalos et al[35]

Abbreviations: ATRA, all-trans retinoic acid; HDAC1, histone deacetylase1; MDR, multidrug resistance; PML, promyelocytic leukemia; RAR, retinoic acid receptor; ROS, reactive oxygen species.

In our works, we designed a series of experiments to investigate the effects of crocetin on proliferation, apoptosis, and differentiation of primary acute promyelocytic leukemia (APL) cells isolated from newly diagnosed APL patients, as well as in NB4 and HL60 cell lines. NB4 cells express the PML-retinoic acid receptor-α (RARα) protein, while HL60 cells are null for this protein. Due to the determining mechanism of the antileukemic effects of crocetin, we investigated the altering activity of tyrosyl DNA phosphodiesterase-1 (TDP1) and histone deacetylase1 (HDAC1), as well as the expressions of PML-RARα, and ABC membrane transporters. Leukemic cells were treated with crocetin (5 to 100 μM), ATRA (0.5 to 10 μM), and arsenic trioxide (As_2O_3, 0.5 to 5 μM) for 3 and 5 days. Cell proliferation, differentiation, and apoptosis were evaluated using several techniques including resazurin, propidium iodide (PI), and annexin-V/PI staining, NBT-Giemsa staining, real-time polymerase chain reaction (RT-PCR), TDP1 activity, Western blot and flow cytometry analysis. Crocetin (100 μM), was observed to significantly inhibit the proliferation and induced apoptosis in primary APL cells, as well as NB4 and HL60 cells like ATRA (10 μM) and As_2O_3 (5 μM) ($P < 0.001$). These proliferation inhibition and apoptosis induction effects were associated with the decreased expressions of prosurvival genes Akt and BCL2, the MDR proteins ABCB1 and ABCC1 and inhibition of TDP1 activity. Meanwhile, the expressions of proapoptotic genes CASP3, CASP9, and Bax were significantly increased. In contrast, crocetin at low concentration (10 μM), like ATRA (1 μM) and As_2O_3 (0.05 μM), induced differentiation of leukemic cells towards granulocytic pattern, and increased the number of differentiated cells expressing CD11b and CD14, while the number of immature cells expressing CD34 or CD33 was decreased. Furthermore, crocetin suppressed the expression of clinical marker PML/RARα in NB4 and primary APL cells, and reduced the expression of HDAC1 in all leukemic cells. The results suggested that crocetin can be considered, alone or in combination with ATRA/As_2O_3, for preclinical and also clinical testing in APL patients.[25] Our other project showed that crocetin could better decrease multidrug resistance proteins (MDR)

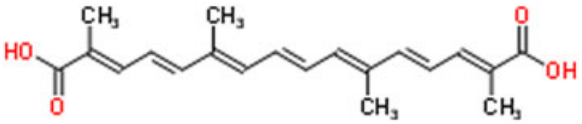

FIGURE 1 2D chemical structure of crocetin

genes comparing the other natural compounds such as epigallocatechin-3-gallate and kaempferol significantly.[37-41]

Nair et al described that LD_{50} and IC_{50} of saffron are greater than 600 mg/kg and 7 to 30 μg/mL, respectively. They reported slightly increase in the serum levels of glutamate pyruvate transaminase, alkaline phosphatase, and the liver/bladder levels of glutathione *S*-transferases in the saffron-treated mice, compared with the control group. Their study showed the antileukemic activity of saffron on lymphocytes might be due to an immunologic-mediated mechanism.[27]

Another study reported 50% cytotoxicity of dimethyl-crocetin 7 to 30 and 11 to 39 mg/mL for CRC on HL60 cells although it could not affect the K562 cells. This report suggested that dimethyl-crocetin could disrupt DNA-protein interactions (eg, topoisomerase II) and inhibit the synthesis of nucleic acids.[28]

4.2 | The antileukemic effect of CRC

Crocin ($C_{44}H_{64}O_{24}$; molecular weight, 976.972 g/mol; PubChem CID, 5281233) is a water-soluble carotenoid which is responsible for the color of saffron. Chemically, CRC is the diester formed from the disaccharide gentiobiose and the dicarboxylic acid crocetin. CRC crystals with a melting point of 186°C dissolve in water and form an orange solution. It has been demonstrated that CRC has antileukemic effects in animal models and cell cultures. The chemical structure of CRC is presented in Figure 2.

Xu et al investigated the proliferative inhibition and apoptosis induction by CRC in human leukemia HL60 cells. The cell viability and morphology of HL60 cells were observed by cell counting and fluorescence microscopy, respectively. The MTT assay, flow cytometer and RT-PCR were used to evaluate the inhibitory effect, cell cycle, and Bax/Bcl-2 expression of HL60 cells, respectively. The results indicated that the growth of HL60 cells was inhibited remarkably in the dose- and time-dependent way. When the CRC concentration was higher than 5 mg/mL, not only the percentage of apoptotic HL60 cells was not increased, case reverse, this percentage decreased due to the cells manifested necrosis. Flow cytometry profiles revealed that cells were blocked in G0/G1phase, the cell proliferation was inhibited obviously at 5 mg/mL concentration of CRC. RT-PCR detection revealed that the expression of Bcl-2 was downregulated strikingly and Bax was upregulated. It is concluded that the CRC can inhibit the proliferation of HL60 cells effectively, and therefore blocks the cells in G_0/G_1 phase. The mechanisms by which CRC induced apoptosis in HL60 cells may be related to the inhibition of Bcl-2 and activation of Bax.[30]

In the other research, Xu et al investigated the effect of CRC on the proliferation and immune function of dendritic cells (DC), which are obtained from the bone marrow of children with acute leukemia. The mononuclear cells were isolated from bone marrow were divided into six groups: blank control group (A), CRC 1.25 mg/mL group (B), cytokines (rhGM-CSF 75 ng/mL + rhIL-4 75 ng/mL + rhTNF-α 50 ng/mL) as group (C), cytokines + CRC 0.3125, 1.25, or 5.0 mg/mL groups (D, E, or F). The numbers of DC were counted, and the phenotypes of DC were determined by flow cytometry on the ninth day of culture. The DC of different groups were mixed with fresh T cells just separated from peripheral blood of children with acute lymphoblastic leukemia, and cultured with rhIL-2 200 U/mL for 5 days. The function of DC was followed up by mixed lymphocyte reaction (MLR). The results indicated that DC numbers in test groups were all higher than those in control group. After 9 days of cultures, the rates of CD1a (+), CD83 (+), and HLA-DR (+) in groups C, D, E, and F were higher than that in group A. There was no statistical difference between A and B groups. MLR showed no rising of the stimulation index of T cells in group A and B, with the increasing of DC. However, the stimulated index of T cells in groups C and E was significantly rising. The stimulation index of T cell in group E was the highest when the number of stimulated cells was the same. They concluded that the capability of DC proliferation induction by CRC is lower than the stimulation by its combination with rhGM-CSF, rhIL-4, and rhTNF-α. However, the CRC can synergically promote the maturity of DCs in cooperation with rhGM-CSF, rhIL-4, and rhTNF-α. The CRC induced DCs can particularly enhance the proliferation of T cells.[29,31]

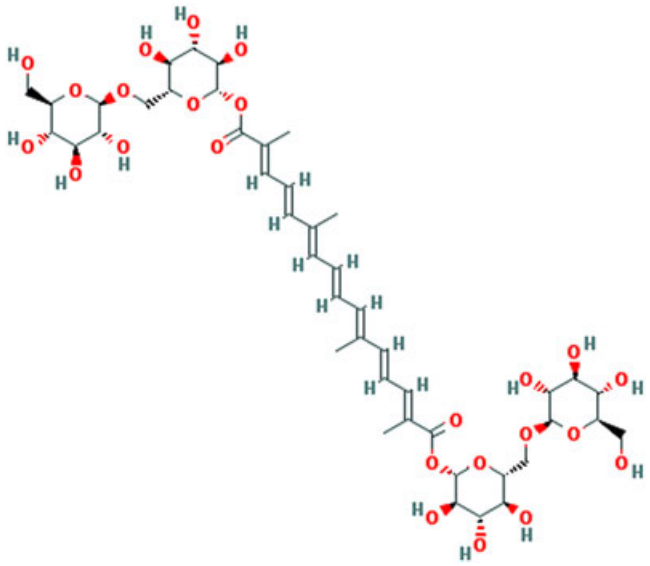

FIGURE 2 2D chemical structure of crocin

A research in 2013, evaluated the effect of CRC (50, 250, and 500 μM) on human T-cell leukemia cell line MOLT-4 at 24 and 48 hours. In this study, the cell viability, apoptotic cells percentage, and reactive oxygen species (ROS) production were evaluated. Results from MTT assay demonstrated that 500 μM CRC significantly reduced cell viability during 48 hours. DNA fragmentation was shown to be significantly increased at higher doses of CRC following 24 and 48 hours. According to their results, while apoptosis was detected at all concentrations, necrosis was detected just at the highest CRC concentration. In comparison with control, ROS production was reduced at 50 and 250 μM CRC concentrations. It is concluded that CRC exhibited mild cytotoxic effects on a leukemia cell line which might be mediated through the increase of DNA fragmentation.[32]

Sun et al investigated different concentrations of CRC on Jurkat cells. They used MTT method for the detection of cell proliferation, annexin-V/PI method for the apoptosis rates, and RT-PCR for Bcl-2 and Bax genes expressions. CRC promoted Jurkat cell apoptosis and inhibited cell growth, in a dose and time-dependent manner. The mechanism might be related to the inhibition of Bcl-2 gene expression and the promotion of Bax gene expression. These results suggest that CRC can be used as a suitable clinical agent for the treatment of T-lineage acute lymphoblastic leukemia.[33]

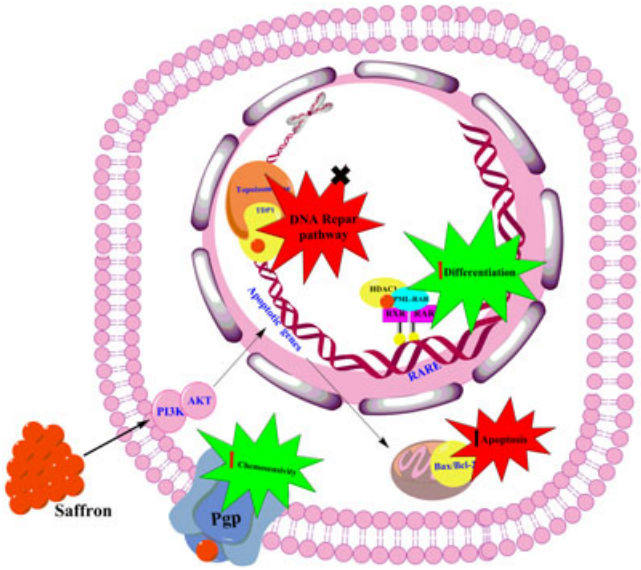

FIGURE 3 Schematic highlighting of the antileukemic effects of saffron on the blastocyst. Saffron suppresses cell proliferation by inhibiting PI3K/AKT pathway and stimulates apoptosis through the intrinsic pathway which then leads to upregulation Bax/Bcl-2. Saffron induces differentiation by the retinoid-related pathway which targets RARE. Saffron enhances chemosensitivity by inhibiting P-gp proteins. Moreover, saffron exerts inhibitory effects on repairing system by targeting TDP1. ↑, increase; ↓, decrease, ×, inhibition; Bax, Bcl-2-like protein 4; Bcl-2, B cell lymphoma 2, HDAC1, histone deacetylase1, PI3K, phosphatidylinositol-4, 5-bisphosphate 3-kinase; PML/RARα, promyelocytic leukemia/retinoic acid receptor-α; RARE, retinoic acid receptor element; TDP1, tyrosyl DNA phosphodiesterase-1

In the other study of Sun et al, the effects of CRC was investigated on HL60 cells in vitro and in vivo. The cells were treated with CRC, and consequently, cell proliferation, apoptosis, and cell cycle profiles were examined by MTT assay, AO/EB staining, and flow cytometry, respectively. In addition, HL60 cells were xenografted into nude mice and treated with CRC in their project. They detected the tumor weight and size, as well as Bcl-2 and Bax expressions by immunohistochemical staining. They showed that CRC (0.625 to 5 mg/mL) inhibits the cell proliferation and increases the apoptosis in a concentration and time-dependent manner. Furthermore, CRC (6.25 and 25 mg/kg) had inhibited the tumor weight and size and Bcl-2 expression while it increased Bax expression in nude mice.[34]

In 2014, the scientists investigated the inhibitory effect of CRC and SFR, on Bcr-Abl protein in K562 cells by in silico as well as the in vitro approaches. In silico molecular docking studies revealed that SFR could be attached to Bcr-Abl protein binding cavity at the same place in which imatinib mesylate was used in the treatment of CML. The predicted polar interactions and hydrophobic contacts constructing a hydrophobic cavity inside the active site, explain the observed inhibitory activity. Cytotoxicity experiments showed that SFR and CRC mediate cytotoxic response to K562 cells. In vitro studies revealed that SFR inhibits the gene expression of Bcr-Abl, while CRC increases the expression.[35]

5 | CONCLUDING REMARKS

Saffron (*Crocus sativus* L.) and its main constituents, crocin, and crocetin can inhibit leukemic cells with different mechanisms including antiproliferative, free radical chain reaction, apoptosis induction, cellular differentiation, and nucleic acid synthesis. Figure 3 summarizes possible mechanisms underlying the antileukemic action of saffron. We propose that saffron increases apoptosis and chemosensitivity via enhancing the ratio of Bax/Bcl-2 and inhibiting multidrug resistance proteins and TDP1 at high concentrations (>50 μM). Saffron also inhibits HDAC1 and PML/RARα, inhibits cell proliferation, and induces differentiation at low concentrations (<10 μM). All these studies encourage more research to evaluate the exact antileukemic mechanism(s) of saffron before confirming by clinical trials. Proposed future projects may be explained as

(1) investigation of pharmacological interaction of saffron with ATRA and whether saffron act via RXR-RAR receptors, (2) investigation of whether saffron may be a synergic agent for valproic acid as HDACi which used as new treatment of leukemia patients, (3) investigation of whether saffron may inhibit topoisomerase I, that could be a synergic agent for doxorubicin, and (4) investigation of molecular mechanisms of action of saffron in leukemic mice.

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