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Review article

Crocus sativus L. (saffron) for cancer chemoprevention: A mini review

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ABSTRACT

Cancer is one of the most feared diseases globally and there has been a sustained rise in its incidence in both developing and developed countries. Despite the growing therapeutic options for patients with cancer, their efficacy is time-limited and non-curative. Hence to overcome these drawbacks, an incessant screening for superior and safer drugs has been ongoing for numerous decades, resulting in the detection of anti-cancer properties of several phytochemicals. Chemoprevention using readily available natural substances from vegetables, fruits, herbs and spices is one of the significantly important approaches for cancer prevention in the present era. Among the spices, *Crocus sativus* L. (saffron; 番紅花 fān hóng huā) has generated interest because pharmacological experiments have established numerous beneficial properties including radical scavenging, anti-mutagenic and immuno-modulating effects. The more powerful components of saffron are crocin, crocetin and safranal. Studies in animal models and with cultured human malignant cell lines have demonstrated antitumor and cancer preventive activities of saffron and its main ingredients. This review provides a brief insight into the anticancer properties of saffron and its components.

1. Introduction

Cancer is one of the most feared diseases globally and there has been a sustained rise in its incidence in both developing and developed countries. It is one of the major noncommunicable diseases posing a threat to world health. Unfortunately, enhancements in socioeconomic circumstances are generally associated with increased cancer incidence. China, India, and Russia, which share rapidly rising cancer incidence, have cancer mortality rates that are nearly twice as high as in the UK or the USA. Vast geographies, growing economies, aging populations, increasingly westernized lifestyles, relatively disenfranchised subpopulations, serious contamination of the environment, and uncontrolled cancer-causing communicable infections have all contributed to its rapid rise in incidence.[1] Under Indian circumstances cancer could lead to severe social and economic consequences, frequently causing family hardships and societal inequity. In a population of ~1.2 billion, nearly > 1 million new cases of cancer are diagnosed every year causing ~600,000–700,000 deaths in 2012.[2] An increasing proportion of the burden is falling on low- and middle-income countries because of not only demographic change, but also a transition in risk factors, whereby the consequences of the globalization of economies and behaviors are adding to an existing burden of cancers of infectious origin.[3] The increasing burden of cancers in low- and middle-income countries (LMICs) is attributable in part to increasing urbanization, expansion of the adult population at risk, and increasing or persistent exposures to infectious agents, tobacco, and dietary deficiencies. Based on the present knowledge of the risk factors it seems that in about 33–50% of cancers primary prevention is principally a helpful method.[4]

2. Cancer projections

A study conducted by D'Souza et al[5] revealed that ~0.44 million died due to cancer during the year 2011, whereas 0.51 million and 0.60 million persons are projected to die from cancer in 2016 and 2021. The projected cancer mortality would escalate to 0.70 million by 2026 because of the change in size and composition of the population. Among women, cancer of the breast, cervix, and ovary account for 34% of all cancer deaths. The leading sites of cancer mortality in males are the lung, esophagus, prostrate, and stomach. The above results show a need for commitment for tackling cancer by reducing risk factors and strengthening the existing screening and treatment facilities.[5] Major contributors to the increase in

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the prevalence of cancer over the years are an increase in the population size as well as an increase in the proportion of elderly population, urbanization, and globalization. The cancer incidence results show an urgent need for strengthening and augmenting the existing diagnostic/treatment facilities, which are inadequate even to tackle the present load.[6]

Since time immemorial cancer has been a topic of exhaustive research both at the molecular as well as pharmaceutical level. Unfortunately, a major concern in successful treatment of cancer is a lack of understanding of the underlying molecular signaling and the probable targets of therapeutics. Despite the growing therapeutic options for patients with cancer, their efficacy is time-limited and noncurative.[7] Since the early 1940s to the present > 50 chemotherapeutic drugs have been discovered for the treatment of cancer. Despite their efficacy the majority of these drugs are associated with severe toxicity leading to physical and mental trauma to patients. Hence, to overcome these drawbacks, an incessant screening for superior and safer drugs has been ongoing for numerous decades, resulting in the detection of anticancer properties of several phytochemicals.[8]

Since millennia nature has been providing us with a vast variety of therapeutic agents. Furthermore, scientists have been able to exploit these natural sources to isolate numerous modern drugs based on their usage pattern of plants in traditional medicine. For cancer prevention and therapeutics, anticancer agents derived from plants and their derivatives have been proven to be effective. For a long time vinca alkaloids either alone or in combination have been used for the treatment of various types of cancers.

Approximately 50–60% cancer patients in the United States utilize agents derived from different parts of plants or nutrients (complementary and alternative medicine), exclusively or concurrently with traditional therapeutic regimes such as chemotherapy and/or radiation therapy. The need for new drugs has prompted studies evaluating possible anticancer agents in fruits, vegetables, herbs, and spices.[7] Chemoprevention using readily available natural substances from vegetables, fruits, herbs, and spices is one of the significantly important approaches for cancer prevention in the present era.

3. Pharmacological properties of saffron

Among the spices, *Crocus sativus* L. (saffron; 番紅花 fān hóng huā) a member of the large family Iridaceae, has generated interest because, besides being used as a flavoring agent, pharmacological experiments have established numerous beneficial properties including radical scavenging, antimutagenic, and immunomodulating effects.[9] Saffron, a spice and a food colorant present in the dry stigmas of the plant *Crocus sativus* L., has been used as a herbal remedy for various ailments including cancer by the ancient Arabian, Indian, and Chinese cultures.[7] In Ayurveda, saffron is used to cure chronic diseases such as asthma and arthritis. It is also useful in treating colds and coughs. Ayurvedic medicines containing saffron are used to treat acne and several skin diseases. A paste of the spice can be used as a dressing for bruises and superficial sores. Ancient texts on Ayurveda have information regarding the herb's use as an aphrodisiac. It is a stimulant. It is largely used as an indigenous medicine across India.[10] The stigma of this plant is also a well known traditional Chinese medicine and is used as safflower to stimulate blood flow and relieve pain by removing stagnated blood.[11]

The pharmacological effects of aqueous or alcoholic extracts of *C. sativus* stigmas have been described in the literature and comprise a wide spectrum of activities, including anticonvulsant, antidepressant, antinociceptive and antiinflammatory, antioxidant, acetylcholinesterase inhibiting, antitussive, reducing withdrawal syndrome, improving male erectile dysfunction, enhancing spatial cognitive abilities after chronic cerebral hypoperfusion, hypotensive, and antisolar properties.[12] Chemical analysis has shown the presence of > 150 components in saffron stigmas. The more powerful components of saffron are crocin, crocetin, and safranal. Studies in animal models and with cultured human malignant cell lines have demonstrated antitumor and cancer preventive activities of saffron and its main ingredients.[13]

The subsequent section provides a brief insight into the anticancer properties of saffron and its components.

4. Anticancer properties of saffron

4.1. Gastric cancer

Gastrointestinal cancers account for 20% of all incident cancers in the United States. The conventional treatment approaches for gastric cancer management include surgery, radiotherapy, and chemotherapy. Substantial amounts of investigations have been carried out to understand the role dietary factors play in the prevention of gastrointestinal cancers, but evidence regarding the potential preventive effect of antioxidants is inconsistent. *In vitro* and *in vivo* studies in animals continue to support the hypothesis that antioxidants reduce the risk of gastrointestinal cancers. However, evidence for the same in human populations is not as supportive.[14]

In the study undertaken by Bathaie et al,[15] the beneficial effect of saffron aqueous extract (SAE) on 1-methyl-3-nitro-1-nitrosoguanidine (MNNG)-induced gastric cancer in rats was explored. SAE administration inhibited the progression of the cancer of the gastric tissue as evidenced by the pathologic data; so that, 20% of cancerous rats treated with higher doses of SAE was completely normal at the end of the experiment and there was no rat with adenoma in the SAE treated groups. Furthermore, the results of the flow cytometry/propidium iodide staining demonstrated that the apoptosis/proliferation ratio was augmented because of the SAE treatment of cancerous rats. Thus the investigators recommend crocin as a potential anticancer agent.[15,16] In a study performed by Hoshyar et al,[17] the mechanism of crocin action was investigated in the gastric adenocarcinoma (AGS) cells. Crocin revealed a dose- and time-dependent cytotoxic effect against an AGS cell line. Crocin-induced apoptosis was substantiated by flow cytometry and assessing caspase activity. The improved sub-G1 population and stimulated caspases in the treated AGS cells confirmed its anticancer effect. Apoptosis was markedly enhanced as demonstrated by raising the Bax/Bcl-2 ratio after crocin treatment.[17]

4.2. Colorectal cancer

In the Western hemisphere colorectal cancer (CRC) is the third most frequently encountered cancer and the incidence rise with increasing age. Surgery, radiation therapy, and chemotherapy are the key components of rectal cancer therapy.[18] In the present era, preventive medicine is becoming a keystone in our model of health. CRC prevention, specially, has become one of the main goals for health care providers, clinicians, and the general public. CRC fits the norm of an ailment appropriate for chemopreventive interventions. It is a ubiquitous disease that is linked with substantial mortality and morbidity rates. CRC has a natural history of transition from precursor to malignant lesion that spans, on average, 15–20 years, providing a window of opportunity for effective interventions and prevention. Current advancement in molecular biology and pharmacology augments the probability that cancer prevention will progressively rely more on chemoprevention. Chemoprevention uses agents to inhibit, delay, or

reverse carcinogenesis. The eventual aim of cancer treatment is suppression of the growth of precancerous and cancerous cells without affecting normal cells and is of particular importance in chemoprevention.[19]

Aung et al[20] suggested that *Crocus sativus* L. (saffron; 番紅花 fān hóng huā) extract and its major constituent, crocin, significantly inhibited the growth of colorectal cancer cells while not affecting normal cells. They demonstrated major concentration-related inhibition effects of the extract on all three colorectal cancer cell lines. Marked antiproliferative effects were also seen in nonsmall cell lung cancer cells. However, *Crocus sativus* extract did not significantly affect the growth of noncancer young adult mouse colon cells. Hence, *Crocus sativus* extract should be investigated further as a viable option in the treatment of colorectal cancer.[20,21]

4.3. Hepatic cancer

Hepatocellular carcinoma (HCC) is the fifth most prevalent cancer and the third leading cause of cancer-related death and its incidence is increasing. The majority of HCC cases are associated with chronic viral hepatitis. With > 170 million individuals chronically infected with hepatitis C virus (HCV) worldwide, HCV is currently a serious global health concern, leading to chronic hepatitis, cirrhosis, and HCC, thereby causing significant morbidity and mortality. With the incidence of HCV infection increasing, the problem of HCV-associated HCC is expected to worsen as well, with the majority of HCCs developing in the setting of cirrhosis.[22] Hepatocellular carcinoma diagnosis and treatment has witnessed many major changes and challenges in the past 2 decades.[23] The limited effectiveness of chemotherapy and the high recurrence rate of cancers highlight the urgent need to identify new molecular targets and to develop new treatments. Numerous epidemiological studies have recently highlighted the existence of an inverse association between fruit and vegetable consumption, natural antioxidants, and cancer risk; in fact, antioxidant intake through diet or supplements of plant origin is strongly recommended for cancer prevention and cure. Hence, cancer can be prevented by the stimulation of the immune system to destroy cancer cells or to block their proliferation.[24]

Saffron significantly reduced the diethylnitrosamine (DEN)-induced increase in the number and the incidence of hepatic dyschromatic nodules in rats. Saffron also diminished the number and the area of placental glutathione S-transferase-positive foci in livers of DEN-treated rats. Besides, saffron counteracted DEN-induced oxidative stress in rats as evaluated by restitution of superoxide dismutase, catalase, and glutathione-S-transferase levels, and decrease of myeloperoxidase activity, malondialdehyde, and protein carbonyl formation in liver. The result of immunohistochemical staining of rat liver demonstrated that saffron inhibited the DEN-mediated elevations in the numbers of cells positive for, cyclooxygenase 2, inducible nitric oxide synthase, nuclear factor-kappa B p-65, and phosphorylated tumor necrosis factor receptor. *In vitro* experiments carried out using HepG2 cells also confirmed these findings and showed inhibition of nuclear factor-kappa B activation, increased cleavage of caspase-3, as well as DNA damage and cell cycle arrest upon saffron treatment. Furthermore, telomerase activity of HepG2 cells reduces after treatment with crocin, which is probably caused by downregulation of the expression of the catalytic subunit of the enzyme. These investigations present verification that saffron exerts an important chemopreventive effect against liver cancer due to the inhibition of cell proliferation and induction of apoptosis. This study also confirms some evidence that saffron protects rat liver from cancer via modulating oxidative damage and suppressing inflammatory response.[25,26]

4.4. Pancreatic cancer

Pancreatic cancer is the fourth leading cause of cancer death with a median survival of 6 months and a dismal 5-year survival rate of 3–5%.[27] Pancreatic cancer (PC) is a lethal disease with a low radical-resection rate and a poor prognosis.[28] As the mortality rate for pancreatic cancer approaches the incidence rate with only 1–4% of all patients surviving 5 years, it would be of great value to provide chemopreventive treatment for high-risk individuals.[29] In spite of recent advances in the current therapeutic modalities such as surgery, radiation, and chemotherapy patients, the average 5-year survival rate remains still < 5%. Recently, compounds from natural sources receive ample attention as anticancer agents. Many epidemiological studies published over the past few decades provide a strong correlation between consumption of vegetables, fruits, or plant derived products and reduced incidence of cancer.[30] With the establishment of outstanding rodent models of pancreatic neoplasia and cancer, there are now systems available for evaluating the role diet, dietary supplements, and/or therapeutic compounds (which can be delivered in the diet) play in disease suppression. Several outstanding reports, which demonstrate clear inhibition or regression of pancreatic tumors following dietary manipulations, represent a noticeable advancement in the field by allowing for the contribution of diet and natural and synthetic compounds to be identified.[31]

A series of experiments were conducted to systematically establish whether crocetin significantly affects pancreatic cancer growth both *in vitro* and/or *in vivo*. For the *in vitro* studies, first, MIA-PaCa-2 cells were administered crocetin and in these sets of experiments, a proliferation assay using H(3)-thymidine incorporation and flow cytometric analysis imply that crocetin inhibited proliferation. Subsequently, cell cycle proteins were evaluated. Cdc-2, Cdc-25C, Cyclin-B1, and epidermal growth factor receptor were modified significantly by crocetin. For the *in vivo* studies, MIA-PaCa-2 as highly aggressive cells than other pancreatic cancer cells used in this study were injected into the right hind leg of the athymic nude mice and crocetin was given orally after the development of a palpable tumor. The *in vivo* results demonstrated significant decrease in tumor growth along with reduction of proliferation as estimated by proliferating cell nuclear antigen and epidermal growth factor receptor expression in the crocetin-treated animals compared with the controls. Both the *in vitro* pancreatic cancer cells and *in vivo* athymic nude mice tumor, apoptosis was significantly induced as pointed by Bax/Bcl-2 ratio. This study provides evidence that crocetin has a significant antitumorigenic effect in both *in vitro* and *in vivo* on pancreatic cancer.[32,33]

4.5. Prostate cancer

A high disease prevalence, the presentation in older age, a frequently slowly progressing course of disease, and high costs make diagnosis and therapy of prostate cancer a special challenge for urologists. Effective prevention of the disease may help to resolve some of the problems mentioned above. The individual risk/benefit ratio of prostate cancer screening is the focus of controversy and currently not in favor of a systematic screening program. Therefore, only prevention could reduce incidence, side effects of treatment, and related mortality. However, it could be expected that pharmaco- or diet-based prevention will be a huge tool for cancer control, even more for prostate cancer burden.[34,35]

In a study conducted by D'Alessandro et al[36] the antiproliferative activity of saffron extract (SE) and its main constituent crocin on five different malignant and two nonmalignant prostate cancer cell lines were determined. Both SE and crocin decreased

cell proliferation in all malignant cell lines in a time- and concentration-dependent manner. Nonmalignant cells were not affected. The majority of cells were arrested at G0/G1 phase with a noteworthy presence of apoptotic cells based on flow cytometry profiles. The expression of Bcl-2 was strikingly downregulated, whereas Bax was upregulated as per the Western blot analysis. Analysis of caspase activity indicated a caspase-dependent pathway with involvement of caspase-9 activation, suggesting an intrinsic pathway. Dependent on these results it is suggested that both SE and crocin can inhibit cell proliferation, arrest cell cycle progression, inducing apoptosis in prostate cancer. Based on these findings investigators recommend that these agents could potentially be used as a chemopreventive as well as a chemotherapeutic agent for prostate cancer management.[36] Furthermore, a preclinical study by Samarghandian and Shabestari[37] (2013) demonstrated a prostate cancer cell line to be highly sensitive to safranal-mediated growth inhibition and apoptotic cell death. Hence it appears to have potential as a therapeutic agent.

4.6. Cervical, ovarian, and breast cancer

The greatest potential for the chemoprevention of cervical cancer is in women with human papillomavirus (HPV) infection, an abnormal screening test, or a noninvasive neoplastic lesion. Potential chemopreventive agents include micronutrients, antiviral agents, and immune modifiers.[38] To investigate the anticancer effect of crocetin, a major ingredient in saffron, and its underlying mechanisms cervical cancer cell line HeLa, nonsmall cell lung cancer cell line A549, and ovarian cancer cell line SKOV3 were treated with crocetin alone or in combination with vincristine. There was a significant inhibition of the proliferation of the three types of cancer cells with crocetin in a concentration-dependent manner. A noteworthy cell cycle arrest through p53-dependent and -independent mechanisms was induced by crocetin. Crocetin caused cytotoxicity by enhancing apoptosis in a time-dependent manner. It also significantly enhanced the cytotoxicity induced by vincristine. Additionally, this synergistic effect was also detected in the vincristine-resistant breast cancer cell line MCF-7/VCR. Thus the investigators suggest that crocetin is a potential anticancer agent, which may be used as a chemotherapeutic drug or as a chemosensitizer for vincristine.[39] Breast cancer remains the leading cause of cancer death among females worldwide. It signifies a shift from the previous decade during which the most common cause of cancer death was cervical cancer. Current treatment modalities, including surgery, radiotherapy, and adjuvant chemotherapy or hormone therapy, have not been successful enough to impart significant improvement in the morbidity or mortality of breast cancer. This cancer is highly resistant to chemotherapy as no effective treatment exists for advanced disease conditions. Along with the existing therapeutic modalities of breast cancer the focus of researchers and clinicians have shifted towards the exploration of the preventive and therapeutic uses of natural products, including dietary phytoconstituents.[40]

Due to the high incidence of breast cancer, optimal strategies for its prevention are imperative. This entails identification of women who are at an increased risk for breast cancer and an integrative approach that includes effective screening methods as well as nutritional, pharmacologic, and surgical management.[41] In India breast and cervical cancers are the most common cancers and have high annual age-adjusted rates in all the registries. In order to have significant improvement in cancer control in India there needs to be a disproportionate focus on women's breast and cervical cancer.[42] In order to determine the effect of crocetin on breast cancer cells, the highly invasive MDA-MB-231 cells were used and their viability measured with the WST-1 assay and the invasiveness through a reconstituted basement membrane. Findings show that crocetin, the main metabolite of crocins, inhibits MDA-MB-231 cell invasiveness via downregulation of MMP expression.[43]

4.7. Skin cancer

The incidence of skin cancer is increasing worldwide. Over the past several decades, attention has been focused on understanding the molecular basis of skin carcinogenesis and identifying substances for use in chemoprevention of skin cancer. Reactive oxygen species generated by chemical carcinogens or UV irradiation play a key role in skin tumorigenesis. Multiple lines of evidence suggest that cellular antioxidant and/or phase-2 detoxification enzymes, collectively known as cytoprotective proteins, can protect against skin carcinogenesis.[44]

These days cancer chemoprevention is recognized as the most hopeful and novel approach to prevent, inhibit, or reverse the processes of carcinogenesis by intervention with natural products. Phytochemicals have antioxidant, antimutagenic, anticarcinogenic, and carcinogen detoxification capabilities thereby considered as efficient chemopreventive agents. Considerable efforts have been done to identify the phytochemicals which may possibly act on one or several molecular targets that modulate cellular processes such as inflammation, immunity, cell cycle progression, and apoptosis. To date, several phytochemicals in the light of chemoprevention have been studied by using suitable skin carcinogenic *in vitro* and *in vivo* models and proven as beneficial for prevention of skin cancer.[45]

The effects of an aqueous infusion of saffron on two stage skin papillogenesis/carcinogenesis in mice initiated by 7-12 dimethylbenz[a]anthracene (DMBA) and promoted with croton oil were evaluated. Marked inhibition in papilloma formation was demonstrated with saffron application in the pre- and postinitiation periods. The suppression could be attributed to the modulatory effects of saffron on some Phase II detoxifying enzymes such as glutathione-S-transferase (GST) and glutathione peroxidase (GPx), as well as catalase (CAT) and superoxide dismutase (SOD).[7,46]

4.8. Lung cancer

Lung cancer is the leading cause of cancer related mortality worldwide largely because in the majority of patients it is at an advanced stage at the time it is discovered, when curative treatment is no longer feasible. Crocetin, saffron plant derivative is known to play a role in cancer chemoprevention. The effects of crocetin were evaluated against lung cancer-bearing mice in both the pre- and postinitiation periods. Crocein treatment normalized the raised levels of lipid peroxidation (LPO) and marker enzymes markedly in carcinogen administered animals. It also raised the activities of the enzymic antioxidants and glutathione metabolizing enzymes. The pathological changes seen in cancerous animals were notably normalized by Crocetin administration.[47]

Samarghandian et al[48] investigated the potential of saffron to induce cytotoxic and apoptotic effects in lung cancer cells (A549). The investigators demonstrated that the proliferation of the A549 cells were reduced following saffron administration in a dose- and time-dependent manner. Furthermore there was an improvement in the percentage of apoptotic cells. The authors suggest that the anticancer activity of the aqueous extract of saffron could be attributed partly to its inhibition of the cell proliferation and induction of apoptosis in cancer cells through caspase-dependent pathways activation.[48]

The potential of the ethanolic extract of saffron to induce cytotoxic and apoptosis effects in carcinomic human alveolar basal epithelial cells (A549), a commonly used cell culture system for

in vitro studies on lung cancer was evaluated. Saffron, in a concentration- and time-dependent manner could reduce the cell viability in the malignant cells. The extract exerts proapoptotic effects in a lung cancer-derived cell line and could be considered as a potential chemotherapeutic agent in lung cancer.[49,50]

4.9. Leukemia

Results of the study conducted by Sun et al[51] demonstrated that crocin suppressed HL-60 cell proliferation and stimulated apoptosis and cell cycle arrest at G0/G1 phase, in a concentration and time-dependent manner. Furthermore, crocin reduced the tumor weight and size of HL-60 xenografts in nude mice, suppressed Bcl-2 expression, and enhanced Bax expression in xenografts.[51] Cytotoxicity experiments conducted by Geromichalos et al[52] demonstrated that safranal (SFR) and crocin mediate cytotoxic response to K562 cells (human chronic myelogenous leukemia cells). SFR and to a lesser extent imatinib mesylate (used in the treatment of human chronic myelogenous leukemia) suppressed the expression of Bcr-Abl gene expressing Bcr-Abl protein tyrosine kinase activity in *in vitro* studies. Additionally, *in silico* molecular docking experiments showed that SFR can be attached to Bcr-Abl protein, positioned within the protein's binding cavity at the same place with imatinib mesylate.[52] Evaluation of the effects of crocin on human T-cell leukemia cell line, MOLT-4, by Rezaee et al[53] demonstrated that crocin exhibited mild cytotoxic effects on a leukemia cell line which might be mediated through the increase of DNA fragmentation.

4.10. Anticancer toxicity

Anticancer treatments such as anthracyclines, though effective, induce cardiotoxicity by releasing radical oxygen species (ROS). ROS generated, respectively, by electrolysis and by Doxo considerably affects cardiovascular function; it reduces ventricular pressure, heart rate, and coronary flow. Augmentation of lipid peroxidation of the myocardium was also demonstrated, whereas superoxide dismutase activity diminished. The myocardial architecture was distorted and the intercellular spaces enlarged. Saffron perfused during electrolysis helps trap ROS and appreciably recovers myocardial function; however, saffron was less effective against Doxo, thus suggesting that mechanisms other than oxidative stress underlie Doxo cardiotoxicity.[54]

4.11. Toxicology

It is also worth noting that the crocin principle of saffron exhibited high efficacy along with no major toxicity in experimental models.[55]

According to LD50 values, safranal was low-toxic in acute intraperitoneal routes and practically nontoxic in acute oral administration in both mice and rats. In subacute toxicity, safranal changed some hematological and biochemical parameters. In hematological tests, a significant decrease in RBC counts, hematocrit, hemoglobin, and platelets were observed. Safranal decreased cholesterol, triglyceride, and alkaline phosphatase. Lactate dehydrogenase and serum urea nitrogen were increased by safranal. Histological studies indicated that safranal did not have any toxic effects on the heart, liver, and spleen. However, pathological changes were seen in the kidney and lung.[56]

5. Discussion and conclusion

Cancer is a major public health concern and its management is frequently unsuccessful. Hence, on-going efforts in the quest for novel agents and therapies to enhance survival are essential. Escalating recurrence of and toxic side-effects of chemotherapeutic agents decrease the clinical efficacy of a majority of anticancer agents that are presently being used. Accordingly, there is forever an invariable requisite to build up alternative or synergistic anticancer drugs with negligible side-effects.

One important approach to extend effective anticancer armamentarium is to investigate the anticancer agents derived from natural sources. Natural compounds, particularly those obtained from plants, have been best explored for their anticancer properties and most of them have been efficient against the known molecular targets of cancer. A substantial number of plant extracts and isolated compounds possess significant antiproliferative or proapoptotic effects. Thus the screening of medicinal plants for anticancer drugs has offered modern medicine with useful cytotoxic pharmaceuticals.

There is better approval by the scientific community that dietary phytochemicals could be promising agents in the fight against cancer. Emerging information has provided fresh insights into the molecular and cellular framework required to set up innovative mechanism-based approaches for cancer prevention by selective bioactive food components.

Cancer prevention by nutraceuticals present in fruits, vegetables, and spices has garnered extensive consideration due to their low cost and wide safety margin. A significant amount of verification from human, animal, and cell culture studies has shown cancer chemopreventive effects from these natural products.

Allopathic medicine commonly practiced currently is only 100 years old. Although traditional medicine has been around for thousands of years, no integration exists between it and allopathic medicine. Ayurveda, the science of long life and one of the most ancient medical systems still practiced on the Indian subcontinent, can be used in combination with modern medicine to provide better treatment of cancer.

Saffron, a spice obtained from the flower of *Crocus sativus*, is rich in carotenoids. Two major natural carotenoids of saffron, crocin and crocetin, are responsible for its color. Preclinical evidence has demonstrated that dietary intake of some carotenoids have potent antitumor effects both *in vitro* and *in vivo*, signifying their potential preventive and/or therapeutic roles in several tissues. The reports represent that the use of carotenoids without the potential for conversion to vitamin A may provide further protection and avoid toxicity.

The mechanisms underlying cancer chemo-preventive activities of carotenoids include modulation of carcinogen metabolism, regulation of cell growth and cell cycle progression, inhibition of cell proliferation, antioxidant activity, immune modulation, enhancement of cell differentiation, stimulation of cell-to-cell gap junction communication, apoptosis, and retinoid-dependent signaling. Various hypotheses for the antitumor actions of saffron and its components have been proposed such as: (1) the inhibitory effect on cellular DNA and RNA synthesis, but not on protein synthesis; (2) the inhibitory effect on free radical chain reactions; (3) the metabolic conversion of naturally occurring carotenoids to retinoids; and (4) the interaction of carotenoids with topoisomerase II, an enzyme involved in cellular DNA-protein interaction (Fig. 1). Additionally, the immunomodulatory activity on driving toward T Helper Cell Type 1 (Th)1 and Th2 limbs of the immune system of saffron was also demonstrated.

Given its therapeutic and economic importance, its natural abundance, in addition to its common usage in ethnic medicine, saffron provides a varied and accessible platform for phytochemical-based drug discovery. A consolidation of its traditional usage as well as its chemical and pharmacological profiles will thus guide efforts aimed at maximizing this potential. A stronger focus on clinical studies and phytochemical definition will be essential for future

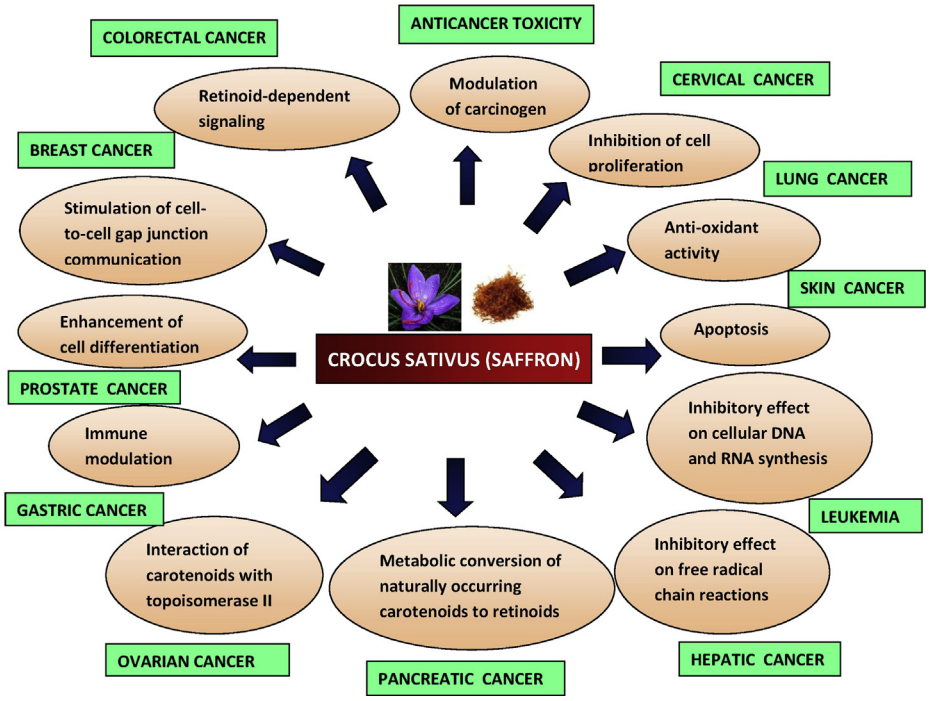

Fig. 1. Crocus sativus Anticancer Mechanisms.

research efforts. Taken together, results and literature data indicate that saffron could be used as a potential cancer chemopreventive agent in clinical trials. However, further direct evidence of anti-cancer efficacy of saffron as a chemo-preventive agent could be obtained from trials that use actual reduction of cancer incidence as the primary endpoint. Hence, it is suggested that future research be warranted that will define the possible use of saffron as an effective anticancer and chemopreventive agent in clinical trials. Although data from *in vitro* studies look convincing, well designed clinical trials in humans are needed to ascertain whether saffron can become part of our armamentarium against cancer.

Promising results in *in vitro* and *in vivo* experiments could open up new avenues for the discovery of the ideal drug combinations of such phytochemicals with synthetic antineoplastic drugs over the conventional combinations of antineoplastic drugs and the possible interventions in the clinical settings.

Conflicts of interest

All authors have no conflicts of interest to declare.

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