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# Saffron: A Comprehensive Review of it's Cancer-Preventive and Curative Properties in Different Types of Cancer

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**ABSTRACT**

Cancer has emerged as an immedicable and fatal disease all around the world. It ranks as the second most common cause of death worldwide. Cancer is estimated by the WHO to be the cause of 1 in 6 deaths. Many modern cancer treatment methods like chemotherapy, photodynamic therapy, catalytic therapy and radiotherapy have been developed, albeit these are restricted, noncurative and generate certain side effects. Therefore, naturopathic medicines are used along with standard treatment procedures as an adjunct to treat cancerous cells without producing any deleterious effects. Due to several bioactive components, *Crocus sativus* L. (saffron) has been utilized in traditional herbal therapy since ancient times. Anticancer activities of saffron and its ingredients-crocin, crocetin, and safranal are established by several workers in various animal models. This review article has focused on the cancer-preventive and curative properties of saffron and its ingredients in different types of cancers, along with pharmaceutical importance and toxicity.

**Keywords:** Saffron, Cancer, Anticancer, Curative, Pharmaceutical, Toxicity.

## INTRODUCTION

Cancer is an emerging health complication across the globe[1]. Modern cancer treatment methods like chemotherapy, catalytic therapy, photodynamic therapy and radiotherapy generate certain side effects, which insisted the researchers to discover other new ways of treatment[1]. Lately, naturopathic medicine has come out as a new alternative treatment option. Naturopathic therapies with the aforementioned standard treatment procedures reduce the reverse effects and increase the reclamation period, improving hunger and sleep quality. It also recovers the damaged cells and tissues and secures the normal cells and tissues. Ample research on consumable fruits, vegetables,

herbs and spices showed that they have many biochemicals, which can be used to minimize cancer[2]. For instance, Digitalins are extracted from purple foxglove (*Digitalis purpurea*, Plantaginaceae); similarly, *Taxus brevifolia*, the pacific yew (Taxaceae) produces taxanes (docetaxel). Hence, several applicable drugs are obtained from plants. Saffron is a high-priced spice across the globe, and it has been used as complementary medicine for centuries[3]. The available literature suggests that the saffron and its ingredients have potential anticancer activity. Many reviews have been established on the biomedical and phytochemical use of saffron in recent times. Saffron possessed carcinoma preventive components, and this was discovered in the beginning of 1990[4]. Numerous review studies on the carcinogenic and tumor-preventive properties of saffron and its ingredients have been published[5]. More current intensive research has provided an updated summary of the pharmacological activities of saffron and its main components.

Saffron is extracted from the dark red dried flowers of the Iridaceae family plants. These plants are mostly grown in dry and mild climate countries e.g. Iran, Turkey and Greece[6]. It is assumed that approximately 190 tons of saffron is produced worldwide, out of which 90% of saffron is produced by Iran alone[7,8]. The cultivation and collection of saffron had been done by hand for thousands of years. That is why the price of saffron is high[9]. Due to the presence of excessive amounts of carotenoid pigments in the stigmas of the saffron flower, it is a reddish-brown or golden-yellow in colour. It has been used as a traditional herbal medicament for several diseases e.g. cardiovascular disorders flatulence, hepatic disorders,and cancer. In the Indian Ayurvedic system, saffron is used as an adaptogen[10]. Several reports suggest that saffron and its bioactive compounds like crocin, picrocrocin, safranal, and crocetin have cancer-preventive qualities and are responsible for stimulation of apoptosis and inhibition of cell proliferation[11,12].

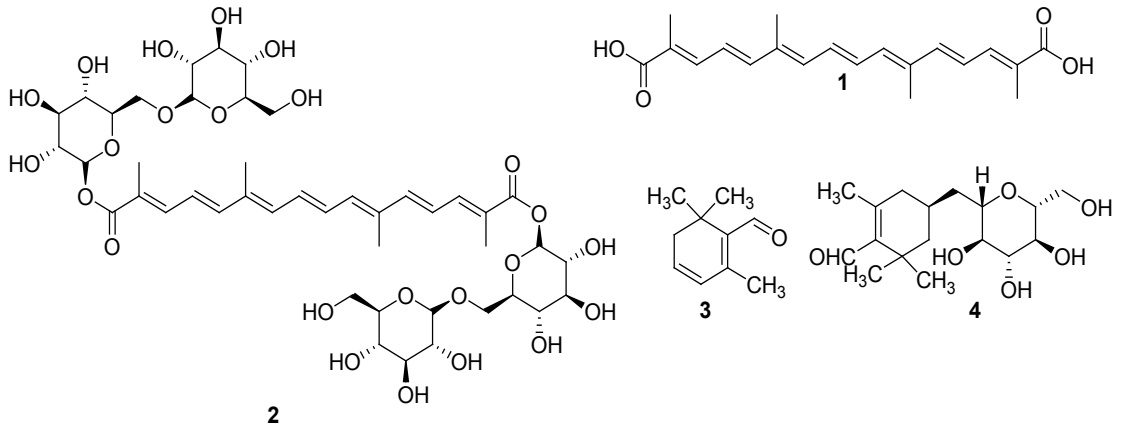


**Fig. 1. Crocetin (1), Crocin (2), Safranal (3), Picrocrocin (4)**

**Chemistry of saffron and its constituents**

Saffron has greater than one hundred and fifty, volatile (safranal and six trimethyl-cyclohexyl derivatives etc.)[13], non-volatile (linolenic, palmitic, oleic, stearic, linoleic and many more)[14] aroma-producing compounds, 56-138 µg/g of riboflavin vitamin,0.7-4 µg/g of thiamine vitamin[15] some pigments like anthocyanin, carotene crocin etc.[1]. A chemical examination of the dried stigma of saffron extract indicates that the principal active carotenoid, secondary metabolites of saffron include monoterpene aldehydes, crocetin, crocin, picrocrocin, and safranal. According to Pfander and Schurtenberger (1982), Zeaxanthin's bio-oxidative splitting is responsible for these components' bio-genesis[16]. The crocin, $C_{44}H_{64}O_2$, M.W. 976.96, is a hydrophilic carotenoid. The dry weight of saffron contains approximately 6% to 16% crocin, which depends on variety, developing environment and refining technique[17]. Crocin is the deep red-coloured constituent, responsible for potent biological activities. Crocin-1($\alpha$-crocin) derived from digentiobiose, is present in plenty quantities. It is a natural colouring agent for food globally[18].

Besides crocin, saffron has many other constituents like crocetin, anthocyanin pigment, $\alpha$-carotene, $\beta$-carotene and zeaxanthin[18]. The

crocetin, $C_{20}H_{24}O_4$, M.W. 328.4, is an amphiphile with low molecular natural carotenoid. Crocetin produces the colour of saffron and is present at the centre of crocin. The dry weight of saffron contains approximately 14% crocetin, which depends on variety, developing environment and refining technique. According to Corradi & Micheli, Duquenois, Sampathu and their co-workers; this carotenoids crocetin or $\alpha$-crocetin and its glycosidic forms as digentiobioside; gentioglucoside, crocin, gentiobioside, diglucoside, glucoside, including $\beta$ and $\gamma$-crocetin, $\alpha$ and $\beta$-carotene, zeaxanthin and lycopene are existed in saffron as main dye materials[19,20,13]. Hence, due to its chemical structure, crocetin mostly shows antioxidant activities.

Picrocrocin, a degradation product of zeaxanthin, discovered by Kajser, is a saffron's chief bitter crystalline terpene-glucoside. The elementary composition of picrocrocin is $C_{16}H_{26}O_7$, with a M.W. of 330.37 g/mol. Picrocrocin is present in high quantities, approximately 1% to 13% in the dry weight of saffron extract[21].

The reaction of picrocrocin and $\beta$-glucosidase releases aglycone 4-hydroxy-2,6,6-trimethyl-1-cyclohexene-1-carboxaldehyde and after losing a water molecule, this aglycone converts into safranal or dheydro-b-cyclocitral[22]. Safranal, main smelling constituent, is produced by natural de-glycosylation of picrocrocin. 2,6,6-trimethyl-1,3-cyclohexadien-1-carboxaldehyde is a cyclical terpenic aldehyde composed of 60% to 70% of volatile components of saffron with the elementary composition $C_{10}H_{14}O$. First, Kuhn and Winterstein discovered that safranal is liberated from picrocrocin by dehydration through enzymatic action[23]. The product of the reaction is safranal, a volatile oil in saffron, and D-glucose. Safranal, M.W. 150.21 g/mol, is a key ingredient that produces the unique smell of saffron[18]. Saffron's and its constituents' stability is depending on temperature, moisture and light. When components of saffron are reserved below -20$^{o}$, the biological activities as a complement do not change for two years or more[9]. Further studies on saffron had revealed that it's other organs, such as pollen, petals[24] and tepals[25] possess following components; Kaempferol, helichrysoside, astragalin, myricetin, kaempferol-3-glycopyranosyl (1→2)-6-acetylglucopyranoside, kaempferol-3-glucopyranosyl (1→2)-glucopyranoside, quercetin, delphinidin-3,5-glucoside and delphinidin.

**Toxicity of saffron and its constituents**

Numerous *in vivo* and *in vitro* research studies have been conducted to decide a non-harming effective dose for humans to treat cancer[26]. A study reports that after consuming 400 mg of saffron for seven days, many haematological and biochemical parameters could be modified but caused no serious changes[27]. Toxicological studies on animal models showed that saffron is less toxic when 20.7g/kg of its oral $LD_{50}$ was given as a decoction. Several studies showed that 0.1 to 5 g/kg saffron extract did not exhibited toxicity in mice. By the Ames/Salmonella testing, it was found that extracted components of saffron, like crocin and dimethyl-crocetin, have no toxicity and are not mutagenic[28]. In the case of sub-acute analysis, saffron exerted no damaging/adverse effects on the liver[29]. *In vitro* studies reported that oral administration of 250 mg/mL of saffron may be deadly for humans[30]. Various clinical studies to determine the acute toxicity of saffron prove that crocin and safranal are non-toxic, and their effective administrable doses are remarkably lower than the toxic doses, confirming their therapeutic activity[31,32]. The high doses of saffron need to be avoided by lactating mothers[33]. When administered orally, the ethanolic extract of saffron caused no signs of mortality/toxicity in mice at 5g/kg[34,35]. Moreover, in a study on rats and mice, safranal was found to be non-toxic when administered orally while low-toxic in IP administration[36]. Thus, it can be deduced that saffron acute exposure is mostly non-toxic. A study to determine the subacute toxicity of ethanolic extract of the stigma of saffron in a dose-dependent manner revealed notable decrement in haemoglobin, HCT levels and red blood corpuscle count, while WBC count, urea, uric acid, creatinine, ALT, AST were found to increase in treated rats. This indicated that saffron's stigma extract causes elevated toxicity[37]. Administration of crocin at 50 mg/kg intraperitoneally in rats for four weeks revealed no cardiotoxicity[38].

**Pharmaceutical importance of saffron and its components**

Many experimental studies have shown that phytochemicals produced from plants have fewer side effects as therapeutic agents than chemically synthesized phytochemicals[39-41]. The saffron and

its components possess many properties such as antioxidant, antigenotoxic, antimutagenic, and tumoricidal, hence can be helpful for the treatment of many diseases like asthma[42], menstruation disorders[43], cardiovascular disease[44], digestive ailments[45], cancer[46], insomnia[47], neurodegenerative disorders, memory impairment and Parkinsonism etc.[5]. Saffron prevents gastrointestinal atonia by modulating the gastrointestinal[48] and potentially treating chronic bronchitis and respiratory disease. Saffron is also used as a therapeutic agent for coughing by working on the alveoli affecting the vagus nerve[49]. Crocin, the major constituent of saffron, has relieved painful dysmenorrhea by modulating the uterine contractions[50]. Saffron's other component, picrocrocin, also behaves as a tranquillizer by inducing a sedative effect on lumbar and spasm pains[51]. Crocetin also effectively treated many diseases such as atherosclerosis[52], haemorrhages[53], alveolar hypoxia[54], arthritis[55], tumours[56] and cell production[57] due to its capability to secure the oxygen transport speed.

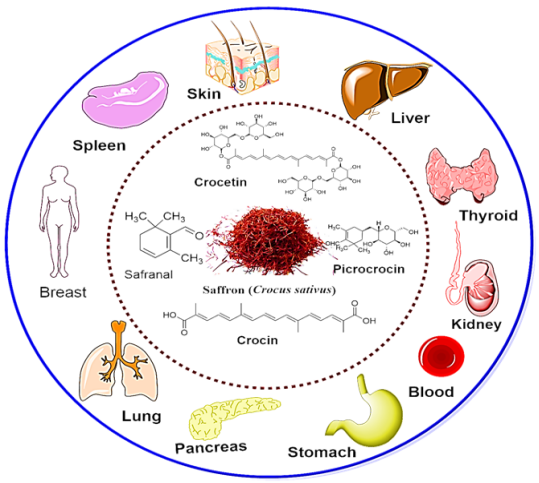


**Fig. 2. Saffron and its major constituents showing cancer preventive activity in various vital organs of body**

## Cancer preventive activity of saffron and its constituents-

In current years, several scientific researchers showed that carcinogenesis could be affected by saffron and its derivative in different types of *in vivo* and important anticancer activities are exhibited in breast, lung, pancreatic, and leukemic cells by crocin and crocetin in *in vitro* systems[57,58]. Research on saffron's ability to prevent cancer in its natural state is few. It has been observed that the sensitivity of saffron and its components varied in different cancer cells because of the presence of unique receptors on the cell surface, intracellular retention transport, variations in drug consumption, unique extraction methods, and variations in cytotoxicity assessment[1]. Bathaie and co-workers reported that high dosage of saffron extract showed no toxicity in 15% of rats[59]. Saffron extract and crocin can inhibit cell proliferation, arrest cell cycle progression, inducing apoptosis in prostate cancer[60]. Numerous experiments of saffron in animals had shown that it significantly reduced the stress caused by diethyl nitrosamine (DEN) in rats[61]. The recent significant literature on anticancer activity of saffron extract and its ingredients are summarized in the Table 1.

### Skin cancer

The growth of ascite tumours, generated from lymphoma ascites of Dalton (DLA), sarcoma-180(S-180), and Ehrlich ascites carcinoma (EAC), was restricted by the appropriate amount of extract of saffron (200 mg/kg). It is also notably extended (2 to 3 fold) the life spans of tumour-suffering Swiss albino mice. Many researchers presumed that stigmas of saffron possessed glycosidic linkage, but they could not ascertain the actual nature of active derivatives of saffron stigmas[62]. In the *in vitro* model, general propagation of lymphocytes was prompted by saffron in the presence of T-cell mitogen[63]. Due to the presence of abundant carotene and vitamin A in saffron, it shows antitumor activities. It is revealed that carotenoids convert in retinol (vitamin A); hence, provitamin activities occur in saffron carotenoids and various evidences attributed the anticarcinogenic activity of carotenoids to β-carotene[64,65]. Lycopene does not have provitamin activity still shows antitumor effects[66-68]. Research conducted *in vivo* revealed that different chemical derivatives of saffron extract inhibited the induction of tumorigenesis. Two-stage beginning/stimulation dimethylbenz-[a]-anthracene (DMBA)-prompted development of skin was impeded by extract of saffron[69]. Its consumption also inhibited soft-tissue sarcomas in mice, induced by the tumor incidence of 20-methylcholanthrene (MCA)[70]. Researchers assumed that this outcome of saffron is associated with the stimulation of the cellular antioxidant systems[71].

Furthermore, the inhibitory effects of hydrated saffron extract depend upon the amount of dose and were obtained on the enlargement of mouse non-neoplastic fibroblast cell lines and human transitional cell carcinoma[72]. Chemo-preventive

activities could be utilized by carotenoids loaded saffron by modulating the, antioxidants, detoxification systems and lipid peroxidation. The initiation of skin tumour was effectively reduced by crocetin. In Swiss-webster mice, it also decreased the development of tumors when combined with croton oil-induced tumors and dimethylbenz-[a]-anthracene (DMBA)[73]. DMBA and croton oil promoted the antitumor action of crocetin in skin tumour-bearing hairless mice[74]. By the demotion of skin tumours in mice with benzopyrene and many other tumours in animals, Crocetin extended an animal's life[75].

**Table 1: Major findings on the anticancer activity of saffron extract and its active components in recent year**

| S. No. | Active Component | Outcome | References |
|---|---|---|---|
| 1 | Stigma aqueous extract | Activates caspase-dependent pathways to cause apoptosis in human lung cancer cells found in the alveolar region. | Samarghandian *et al.,* 2013 |
| 2 | Crocin | Noteworthy ability to significantly inhibit the growth of human prostate cancer cell types. | D'Alessandro, *et al.,* 2013 |
| 3 | Saffron | Inhibits cell growth and induces apoptosis in liver cancer. | Amin *et al.,* 2011 |
| 4 | Saffron extract & crocin | Both *in vitro* and *in vivo* models have demonstrated notable cancer chemopreventive effects. | Zhang *et al.,* 2013 |
| 5 | Crocin | Crocin reduced the overexpression of Bax and the downregulation of Bcl-2, hence reducing apoptosis. | Mehri *et al.,* 2012 |
| 6 | Crocin | In HeLa and MCF-7 cells, induces cell death; liposomal encapsulation enhanced the cytotoxic effects. | Mousvi *et al.,* 2011 |
| 7 | Crocetin | The three different kinds of cancer cells' growth was greatly suppressed, in a concentration-dependent manner, by treating them with crocetin (60-240 µmol/L) for 48 hours. | Zhong *et al.,* 2011 |
| 8 | Ethanolic extract of saffron | Malignant cells viability was lowered in a concentration- and time-dependent way. | Samarghandian *et al.,* 2010 |
| 9 | Ethanolic extract of saffron | Induces cytotoxicity and apoptosis in human alveolar basal epithelial cells with cancer (A549). | Samarghandian *et al.,* 2011 |
| 10 | Crocetin | MDA-MB-231 cell invasiveness is inhibited through the down regulation of MMP expression. | Chryssanthi *et al.,* 2011 |
| 11 | Saffron extract | In HCT116 p53 wildtype cells, generated a p53-dependent pattern of cell cycle distribution with a complete G2/M halt. | Bajbouj *et al.,* 2012 |
| 12 | Crocin | HepG2 cells telomerase activity declines. | Noureini *et al.,* 2012 |
| 13 | Crocin | BxPC-3 cells undergo apoptosis and G1-phase cell cycle arrest. | Bakshi *et al.,* 2010 |
| 14 | Aqueous extract of saffron | Suppresses cancer cell growth and induces apoptosis by activation of caspase-dependent pathways. | Samarghandian *et al.,* 2013 |
| 15 | Crocetin | Induces apoptosis, shows anti-proliferative, and antioxidant properties against stomach cancer. | Bathaie *et al.,* 2013 |
| 16 | Crocin | The Bax/Bcl-2 ratio increased considerably suggesting a considerable stimulation of apoptosis. | Hoshyar *et al.,* 2013 |
| 17 | Crocin | At a dosage of 10 mM inhibited the growth of HCT116 wild-type and HCT116 p53–/–cell lines. | Amin *et al.,* 2015 |
| 18 | Saffron extract and crocin | Suppress cell division, halt the development of the cell cycle, and trigger apoptosis in prostate cancer cell lines. | Alessandro *et al.,* 2013 |
| 19 | Saffron extract, crocetin and crocin | Inhibited the migration and invasion of prostate cancer cells by downregulating the expression and activity of urokinase and metalloproteinase. | Festuccia *et al.,* 2014 |
| 20 | Crocin | Enhanced the rate of apoptosis and the fraction of HO-8910 cells in the G0/G1 phase. Up-regulate the expression of p53, Fas/APO-1, and Caspase-3. | Xia *et al.,* 2015 |
| 21 | A new drug, trans sodium crocetinate | Glioblastoma multiforme treated better during radiation therapy. | Gainer *et al.,* 2015 |

**Leukemia**

*In vitro* studies revealed that crocin, a main anticancer component of saffron, prevented human chronic myelogenous leukemia K562 and promyelocytic leukaemia HL-60 cells from growing by using crocin, dimethyl-crocetin and crocetin; the 50% inhibition ($ID_{50}$) tended to occur at 0.8 and 2 mM doses[76]. The range of concentrations at which

dimethyl crocetin and crocin acquire 50% cytotoxicity is 7–30 mg/mL and 11–39 mg/mL, respectively, and this is reported to different cancer cell lines such as P388 leukaemia andL1210 leukaemia[63]. It has been noted that topoisomerase II and other DNA-protein interactions are critical for the production of cellular DNA, which could be interrupted by dimethyl-crocetin. In mouse bone marrow micro-nucleus tests, mitomycin-C (MMC), cisplatin (CIS) and urethane (URE) produced genotoxicity, which is significantly impeded by saffron extract[77]. Prem Kumar *et al.,* advocated that extract of saffron possessed carotenoids and showed anticarcinogenic effects in Swiss albino mice[78]. Eldaly in 1998 revealed that cisplatin-induced toxicity in rats like nephrotoxicity and cysteine (20 mg/kg body weight) and saffron extract (50 mg/kg body weight) both reduced the alteration in enzyme activity[79].

**Cervical cancer**

Cervical epithelioid carcinoma-derived HeLa cell responded quickly toward the way saffron inhibits the production of DNA and RNA[80]. Extract of saffron inhibited the synthesis of cellular nucleic acid in HeLa cells[81]. In contrast to ROS (reactive oxygen species), apoptosis was a major factor in saffron's lethal effect on HeLa cell lines[82]. Liposomal encapsulation enhanced the effect of crocin on malignant cells by triggering apoptosis. Cell death is caused by crocin and its liposomes in HeLa cells[83]. A study on HeLa cells indicated that in vitro expansion of HeLa cells was mainly driven by crocin with $LD_{50}$ of 3mM. Additionally, it was shown that even at large dosages, crocetin did not inhibit cell proliferation[84]. Further, Abdullaev in 1994 reported that crocetin did not affect colony formation in HeLa cells.

On the contrary, other workers reported that crocetin exhibited a cytotoxic effect against a cancer cell line obtained from a non-solid tumour[65,85], distinct human primary cells from surgical specimens and various tumor cell lines[28]. HeLa cells treated with crocin showed vacuolated areas, shrinkage, size decrease, and pyknotic nuclei, according to microscopic examination. The program cell death pathways were activated in crocin-treated HeLa cells[84,86]. Crocetin exhibited the anti-proliferation effect, which depended on its concentration. Crocetin induced p21(WAF1/Cip1) and p53-dependent and independent processes that led to cell cycle arrest. Consequently, the antitumor effect of crocetin in 3 types of cancer cell was shown by induced apoptosis. The cytotoxic effect of vincristine could be increased by crocetin[87]. Recently, Abdullaev and Frenkel concluded that compared to normal cells, malignant cells such as normal lung fibroblasts WI-38, lung tumor-derived A549 cells and VA-13 cells were inhibited more by saffron in the synthesis of DNA and RNA. *In vitro*, saffron extract increased the number of mature and immature lymphocytes and created a colony of healthy human lung cells[63,80,81]. According to another report, saffron extract showed pro-apoptotic effects on alveolar basal epithelial cells. Many outcomes showed that saffron possessed a toxic effect due to induction of A549 cells apoptosis in concentration-dependent mode. The cell could be diminished by saffron-induced apoptosis in the A549[88].

Crocetin impedes lipid peroxidation and enhances the action of GSH-Px, GST, superoxide dismutase and catalase, which makes it evident that it acts as a radical scavenger. Hence it exhibited the anticancer effects in lung cancer animal models by induced drug-metabolizing enzyme activity[89]. Marker enzymes like lactate dehydrogenase LDH, arylhydrocarbon-hydroxylase AHH, adenosine deaminase ADA, GGT and 5-nucleotidase were reduced by crocetin and associated with carcinogen followed benzo[a]pyrene administration in tissues of lung[89]. Additionally, Magesh and their co-workers[90] reported that crocetin impeded the propagation of lung cancer cells as calculated through producing glycoproteins, cell nuclear antigen PCNA and polyamine synthesis.

**Breast cancer**

It has been discovered that human breast cancer cells (MCF-7) undergo apoptosis was prompted by saffron and crocetin through p53-mediated activation of apoptosis. Saffron induced the caspase-dependent pathway in Bax protein expression andin MCF-7 cells[91].

A 2011, study by Samarghandian *et al.,* showed that the ethanolic extract of saffron had pro-apoptotic effects in lung cancer cell line and antiproliferative and cytotoxic effects in carcinomic alveolar basal epithelial cells.

It is safe for L929 at high concentrations and is a good chemotherapeutic agent for lung cancer[92]. Using the flow cytometry approach, the impact of crocin and its nano liposomal formulation on estrogen receptor based human cancer cells was assessed by measuring the percentage of apoptotic cells. Cell death and improvement in cytotoxic effects could be caused by liposomal encapsulation in MCF-7 cells[83]. Crocetin inhibited the breast cancer cells in a concentration-dependent approach, and this effect is estrogen-receptor independent. Crocetin is an important metabolite of crocin. The invasiveness of estrogen receptor independent breast cancer cell is inhibited by crocetin through down-regulating the MMP expression. Hence it is used as a chemo-defensive agent in breast cancer[93].

**Colorectal cancer**

According to a number of researches, saffron caused apoptosis and DNA damage in p53 isogenic HCT116 cell lines. The apoptogenic effect has been delayed by autophagy in HCT116 p53-/- cells. A functional p53 inactivation is shown in many tumours[94]. The proliferation of cancer cells in the colon was significantly impeded by saffron and its component crocin, but has no impact on normal cells[95]. Subcutaneous injection of DHD/K12-PROb cells from rats with adenocarcinoma induced colon cancer in rats, and this tumour growth was reduced by crocin (400mg/kg body) in female rats. Hormonal factors played an important role in the selective anticancer activity in female rats compared to male rate[96].

**Liver cancer**

Several studies showed that saffron significantly exhibited chemo-preventive activities alongside diethylnitrosamine increased liver cancer by inhibiting cell propagation through inducing apoptosis, regulating oxidative injure and reducing provocative reaction. Saffron inhibited the nuclear factor-kappa B activation induced cleavage of caspase-3, DNA injure, and cell cycle seize[63]. Apoptosis is more effective in comparison to ROS in the HepG2 cell lines[92]. Crocin showed the antiproliferative effects on liver cancer cells. It decreased the catalytic subunit expression of the enzyme, which in turn decreased the telomerase activity of liver cancer cells[96]. Crocetin prevented the cytotoxicity induced by aflatoxin, and in C3H10T1/2 fibroblast cells, rat liver microsomes generated a DNA adduct[97]. *In-vitro*, crocetin reduced the formation of AFB1-DNA adduct. AFB1-induced hepatic damage and AFB1-DNA adduct formation were protected by crocetin in rats through the raising the hepatic GST, GSH and GSH-Px[98]. Crocetin reduced the activities of serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and gamma-glutamyltranspeptidase (GGT), indicating the suppression of AFB1-prompted hepatotoxic lesions in rats[99]. Crocetin exerted the inhibitory effect on benzo[a]pyrene-induced genotoxicity and neoplastic formation in C3H1oT1/2 cells by increasing the GSH activity and decreasing the benzo[a]pyrene-DNA adducts formation[100]. Crocetin indicated an inhibitory effect on the development of malondialdehyde (MDA), by increasing reactive oxygen species (ROS), generated in primary hepatocytes[101]. Hence, crocetin showed protective effects on ROS by scavenging the free radical[100,101].

**Pancreatic cancer**

Crocin, exerted apoptotic effects in human pancreatic cancer cell lines (BxPC-3). The crocin-mediated growth inhibition and apoptotic was reported in pancreatic cancer cell lines[102]. Several *in-vivo* as well as *in-vitro* investigation srevealed that crocetin exerted impressive anticarcinogenic effects in pancreatic cancer cells via inducing apoptosis. Proteins of the cell cycle and epidermal growth factor receptorare impressively changed by the administration of crocetin in a pancreatic cell line (MLA-PaCa-2). In an *in-vivo* experiment, crocetin significantly down-regulated the tumour growth with inhibition of proliferation. In both *in-vivo* athymic nude mice tumours and *in vitro* pancreatic cancer cells, apoptosis was effectively encouraged, represented by Bax/Bcl-2 ratio[103].

**Lung cancer**

As stated by Samarghandian and their co-workers, the extract of saffron in ethanol impeded the cell viability in alveolar basal epithelial carcinoma cell line in humans. This ethanolic extract of saffron could be an effective chemotherapeutic agent[92]. Additionally, the hydrated extract of saffron showed cytotoxic effects by prompting apoptotic effects and impeding cell proliferation by enhancing Caspase-dependent pathways' activity in the A549 cells[104].

**Cancer of digestive system**

In human and rat adenocarcinoma gastric cancer cells, crocetin stimulated apoptotic effects, down-regulated Bcl-2 and induced Bax expression[105]. Besides it, in the gastric adenocarcinoma cells, an apoptotic effect was induced by Crocin. Crocin-induced apoptosis is indicated by the increment in the Bax/Bcl-2 ratio. Autophagy-free classical apoptosis was stimulated by Crocin in colon cancer cells[107].

**Cancer of reproductive organs**

Crocin, a crucial component of saffron, inhibited cell proliferation in prostate cancer cell lines. The expression of Bcl-2 could be down-regulated by crocin and saffron extract, but the Bax could be up-regulated by crocin and saffron extract[108]. Saffron, crocetin and crocin inhibited the migration of prostate cancer cells by down-regulating the expression of metalloproteinase and urokinase, which indicates that these agents can arrest the metastatic process[109]. Crocin might significantly repress the growth of ovarian cancer cells and arrest these cells in the G0/G1 phase and stimulate the apoptosis through up-regulating Fas and p53 and expression and enhancing the activity of caspase-3-regulated apoptotic pathway[110].

**Clinical trials of saffron**

It has been advocated that saffron and its crucial components, e.g. crocetin, crocin, safranal and picrocrocin, possess cancer-preventive activities. Numerous *in-vivo* and *in-vitro* preclinical tests suggested that saffron and its natural components are better adjuvant medicines to prevent cancer with almost no reverse effects. But still, it has not been tested on humans on a large scale; simultaneously, first clinical trial data published on cancer-preventive activities of saffron in the Avicenna journal of Phytomedicine (AJP) and it is based on the cancer-preventive activities of saffron along with chemotherapy in liver cancer afflicted patient[111]. 50 mg dose of saffron showed effective cancer-preventive activities on patients with primary cancer along with cancer of various organs e.g. oesophagus, colon, ovarian, stomach and breast. The effectiveness of this medicament was analyzed by CT scan. Trans-sodium crocetinate is recently identified as a glioblastoma (GBM) along with associated radiation therapy[112].

**Future prospective**

Saffron is used in the form of the spice from ancient times. In addition to this, it has been used as a medicine in Indian Ayurveda system from a very long time. Saffron exhibits no harmful effects on normal cells in comparison to other expensive modern cancer treatment methods. Unfortunately, there are no comprehensive and methodical studies on the anti-carcinogenic properties of saffron are available. Hence, epidemiological and in-depth studies are required to analyze the molecular mechanism and various biological active components of saffron, which exhibits effective cancer-preventive activities, and to examine the drug delivery system. Additionally, more clinical trials on animal models and humans will be conducted to determine saffron's efficient, non-toxic dose. Hence future researches should be performed to develop new therapeutic constituents in saffron through biotechnological methods, including enzyme conversion, callus induction and elicitation in the company of natural ingredients and to examine the nano particle's application of saffron ingredients drug. Thus, it can be expected that saffron alone or in combination with other phytochemicals will emerge as a potent anticancer drug, and this emerging platform of a new scientific discipline may be known as SAFFRONOLOGY.

## CONCLUSION

The modern methods of cancer treatment have not only exerted harmful effects on normal cells but are not completely effective. In the search of an adjuvant drug for cancer treatment, the attention of researchers turned towards saffron's cancer-preventive properties. Due to presence of numerous volatile, non-volatile, aroma-generative compounds, vitamins, minerals, many pigments and proteins, saffron and its principal components are used to treat different types of diseases and disorders. Various *in vivo* and *in vitro* experiments in animal models have proved that saffron possesses potent cancer preventive activities without any severe toxicity. A few clinical trials of saffron on animals and humans have been conducted to determine its safety dose. However, we need to work on more clinical trials of saffron on cancer-afflicted humans on a large scale to know its efficacy as an adjuvant for anticancer herbal medicine in the near future.

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**Conflict of Interest**

The authors declare no conflict of interest.

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