

An Updated Overview of the Treatment of Colorectal and Gastric Cancer Using Saffron

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Abstract: Despite the increasing number of drugs and treatments available for cancer patients, the effect of cancer on the quality of life of patients and their life expectancy is significant. Moreover, many new therapeutic options have shown to have adverse effects without improving outcomes. These days, natural plants and chemopreventive drugs are commonly used. Chemoprevention is a new form of therapy that targets specific premalignant-malignant transformations. Plant-derived substances, such as polyphenols, flavonoids, carotenoids, alkaloids, etc., have a range of biological effects. Despite extensive studies on the anti-inflammatory effect of saffron carotenoids, they are also bioactive in some other ways, including the inhibition of tumor growth and the induction of cell death. In addition to interfering with a wide array of signaling molecules, this substance has pleiotropic effects: it inhibits pro-inflammatory molecules, transcription factors, enzymes, protein kinases, protein transport proteins, proteins that are crucial for cell survival, growth factors, proteins that regulate the cell cycle, and chemokines. Saffron has high oral bioavailability and is, therefore, suitable for treating gastrointestinal diseases. This antioxidant and anti-proliferative property of saffron makes it a promising chemopreventive agent for colorectal cancer. In contrast with in vitro studies devoted to saffron and in vivo studies on animal models, saffron has rarely been assessed in clinical studies dealing with gastrointestinal oncology. However, several clinical trials are in progress in this domain, although saffron has no approved medical indication as of yet.

Keywords: Saffron; Colorectal cancer; Gastric cancer; Chemoprevention; Treatment

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1. Introduction

Cancer is the second most common cause of death in Western countries. An evolving sequence causes an adenoma to develop into cancer over the course of around 10 years^[1,2]. A malignant transformation results from several steps that involve mutations at the germinal and somatic levels. Chemopreventive agents may be effective for patients who are still in the early stages of cancer^[3]. Studies have shown that non-steroidal anti-inflammatory drugs (NSAIDs), such as low-dose aspirin, sulindac, and celecoxib, can help prevent colon adenomas secondary to primary occurrence^[4,5]. In terms of chemoprevention, saffron has been touted as one of the most promising substances for chemoprevention^[6].

In plant-based food and medicinal herbs, there are three main compounds – alkaloids, phenylpropanoids, and isoprenoids – all of which are essential to human health and nutrition [7,8]. The food and beverages derived from plants are also known as functional food and beverages, which are mainly fruits, vegetables, herbs, and spices [9]. For nearly 3,000 years, dried styles from *Crocus sativus* flowers have been used in traditional medicine across many continents, cultures, and civilizations [10,11].

Aside from its distinctive aroma, color, and taste, saffron is cultivated all around the world, particularly in Iran [12]. Chemoprotective agents work by enhancing endogenous mechanisms against different stages of cancer development using exogenous phytochemicals. Herbal and plant-based chemopreventive properties have received much attention [13,14]. An extract of saffron, for example, could contribute greatly to the development of effective chemopreventive treatments [15,16].

Saffron has demonstrated anticancer and antitumor properties in both animal models and cell lines [17-18]. Various hypotheses have been proposed as to why saffron and its ingredients may have anti-carcinogenic and antitumor properties: (1) inhibition of DNA and RNA synthesis, but not protein synthesis [17]; (2) free radical scavenging [19]; (3) regulation of retinoid synthesis [20]; (4) interaction between carotenoids and topoisomerase II, which is an enzyme that helps regulate DNA-protein interactions [17]; (5) stimulation of interactions via lectin [21].

2. Safety of saffron

Saffron and two of its most active components, crocin and crocetin, are devoid of side effects when used at a daily dose of up to 100 mg as part of an Iranian regime for 26 weeks. Besides allergic reactions, drowsiness, stomach problems, nausea, and vomiting seem to be some of the common side effects of saffron. Saffron has been recently approved as a natural food dressing and flavoring by FDA [22]. Consumed in large quantities, it may be unsafe. When doses exceed five grams, poisoning can occur, and in some cases, 12-20 grams can be fatal.

3. Anticancer and chemopreventive properties of saffron

Evidence from literatures demonstrates that saffron extract has chemopreventive properties. Various molecular mechanisms contribute to chemoprevention: (1) DNA, RNA, and proteins are downregulated; (2) free radicals are reduced or detoxified; (3) retinoids are metabolically converted [23]; (4) lectin interactions directly or indirectly regulate topoisomerase II; (5) hTERT (human telomerase catalytic subunit expression) is downregulated [24]. Based on in vitro and in vivo models, saffron extract has been found to promote cancer prevention in various types of cancers, including colorectal, lung, cervical, skin, pancreatic, ovarian, prostate, breast, blood, liver, bladder, gastric, and esophageal. Various studies have provided evidence of these effects.

4. Colorectal cancer

The first in vivo study on saffron extract containing crocin, conducted by Garcia-Olmo and his coworkers, was performed on colorectal cancer in 1999 [23]. A subsequent study by Abdullaev and his coworkers evaluated the efficacy of crocetin on colorectal cancer cells by examining different compounds extracted from saffron [24]. Thereafter, saffron extract was also found to inhibit colorectal cancer cells in a p53-independent manner [25]. Crocetin was found to inhibit the proliferation of colorectal cancer cells in SW480 cell line in a dose-dependent manner via a p53-independent and p21-dependent mechanism [26,27], causing apoptosis and reducing DNA repair over time [28]. Crocetin-mediated apoptosis occurs when the p53-induced death domain (PIDD) and FAS-associated death domain proteins are activated [29]. The administration of crocin was shown to have a robust anti-proliferative effect on normal cells but little or no effect on cancer cells in human colorectal cancer models (HCT116, HCT115, and SW480) [30]. Upon

subcutaneous inoculation of DHD/K12/PROb cells and treatment of female rats with crocin (400 mg/kg i.p.), a substantial reduction in tumor size was observed, confirming that crocin has antitumor effects on colorectal cancer cells [26]. In addition, the use of liposomal encapsulated crocin compared to free crocin in mice carrying C26 colon carcinoma resulted in a superior antitumor response compared to that seen with free crocin injected into the mice [31].

In another study performed by Bajbouj and other researchers, it was demonstrated that crocin inhibited the proliferation of both HCT116 wildtype and HCT116 p53 $-/-$ cell lines at a specific concentration [28]. The distribution of wildtype cells in HCT116 after 24 hours and 48 hours of crocin treatment showed an accumulation in G1 (55.9%, 56.1%) compared with the control (30.4%). After 24 hours, there was no significant inhibition of HCT116 p53 $-/-$ cell growth by crocin. As a result of crocin's inhibition of autophagy in HCT116 cells with p53, crocin led to the formation of light chain 3 (LC3)-II as well as a noticeable decrease in Beclin 1 and Atg7 protein levels. Compared with crocin exposure alone, p62 levels in the cells increased significantly after Bafilomycin A1 (Baf) and crocin treatment. In addition, apoptosis was induced in wildtype HCT116 cells by Baf pretreatment, as revealed by annexin V staining. While Baf-exposed HCT116 p53 $-/-$ cells collected DNA damage sensors, crocin-exposed cells did not initiate apoptosis, suggesting that autophagy is not required for crocin-induced cell death.

According to Barel and other researchers, although there is inherent variability between observers regarding the evaluation of single factors and that of combined parameters in endoscopically removed pT1 colorectal cancer, the impact of this variability on the risk of not performing surgery in a patient is minimal [32]. According to the pT1-specific international colorectal cancer guidelines, several parameters related to the risk of tumor recurrence have been evaluated using hematoxylin-eosin-saffron (HES) and immunohistochemistry slides. Compared with HES slides, cytokeratin immunohistochemistry reached an excellent agreement in tumor budding quantification. Furthermore, the dual-color immunohistochemistry of cytokeratin and podoplanin improved the accuracy of lymphovascular invasion detection. Researchers have found that acceptable interobserver agreement can be achieved when evaluating risk of recurrence following endoscopic removal of pT1 colorectal cancer. Besides HES slides, immunohistochemistry could be helpful in detecting tumor budding and lymphovascular invasion.

The cytotoxic and multidrug resistance reversing agents derived from saffron natural monoterpene in colon cancer cells were also investigated in another study [33]. TMPE was identified as an effective MDR modulator in doxorubicin-resistant cancer cells and displayed selective cytotoxicity against doxorubicin-resistant colon cancer cells. It was reported that combining TMPE derivative with doxorubicin leads to the transport activity of ABCB1 protein being inhibited without affecting the level of expression. Based on molecular modeling, TMPE was shown to be a more reactive molecule than the parent compound β -cyclocitral. From the analysis of electrostatic potential maps of both compounds, it was hypothesized that the lower general toxicity of β -cyclocitral owes to its reduced reactivity and susceptibility to electrophilic attacks. TMPE was shown to reverse MDR in cancer cells.

Gullu's work examined how compounds containing saffron can inhibit MACC1-dependent cell proliferation and migration of colorectal cancer cells [34]. Using metastasis-associated in colon cancer 1 (MACC1)-induced cancer cell growth and motility as a model, they investigated the inhibitory effects of saffron. The MACC1-expressing colorectal cancer cells were restricted by saffron crudes in a concentration- and dose-dependent manner. At the G2/M phase, saffron does not induce apoptosis or delays cell cycle progression. Rescue experiments have found reverse effects. MACC1 and DCLK1 interact in various tumor entities and contribute to metastasis formation. Following that, crocin in saffron extracts reduces DCLK1. As a result of DCLK1 downregulation, saffron inhibits proliferation and migration in MACC1-expressing cells. The purpose of this study was to identify compounds containing saffron that could inhibit the proliferation and motility of cancer cells through the novel target MACC1.

In another recent study conducted by Amin and other researchers, they investigated the effects of saffron and its constituents on colorectal cancer cell lines with defective mismatch repair (dMMR) [35]. They examined saffron crude extracts – safranal and crocin – in the human colorectal cancer cell lines: HCT116, HCT116+5 (inserted MSH3), HCT116+3 (inserted MLH1), and HCT116+3+5 (inserted MLH1 and MSH3). Cytotoxicity and proliferation were analyzed by MTT assay, and TPDP1, CDC25b, p-H2AX, and GAPDH were analyzed using Western blot. The saffron crude extracts reduced colon cell proliferation by 70% compared to cells with proficient MMR, and the wound healing assay showed that cells with deficient MMR do better (up to 90%). Caspases 3 and 7 were upregulated with the reduction in cellular proliferation, which was supposed to be the effect of safranal and crocin. It was concluded that saffron has a significant anti-proliferative effect in cells with deficient MMR. **Table 1** summarizes the findings of several studies using saffron against colorectal cancer.

Table 1. Saffron against colorectal cancer

Agent	Cell type or species	Effects	Reference
Crocus sativus extract	HCT116, SW480, and HT-29	Significantly inhibits the growth of colorectal cancer cells	Vajravijayan S, 2016 [24]
Crocic	HCT116, SW480, and HT-29	Significantly inhibits the growth of colorectal cancer cells	Bajbouj K, 2012 [25];
Crocic	Mice	Suppresses chemically induced colitis-related colon carcinogenesis	Garcia-Olmo DC, 1999 [26]; Abdullaev Jafarova F, 2002 [27]
Crocetin	HCT116 cell	Inhibits the growth of colorectal cancer cells	Koch A, 2015 [28]
Crocetin	SW480 cells	Induces cytotoxicity in SW480 cells	Ray P, 2016 [29]
Crocic	CT26 cells	Antitumor activity in colorectal cancer cells	Li CY, 2012 [30]
Saffron aqueous extract	HCT116 wild cell and HCT116 p53 cell lines	Induces DNA damage	Rastgoo M, 2013 [31]
Crocic	HCT116 wild cell and HCT116 p53 cell lines	Promotes a decrease in cell proliferation	Koch A, 2015 [28]
Safranal and Crocin	HCT116	Induces anti-proliferation in cells with deficient MMR	Barel F, 2019 [32]
Saffron aqueous extract	MACC1 and DCLK1	Inhibits the proliferation and motility of cancer cells	Sroda-Pomianek K, 2020 [33]

5. Gastric cancer

Chemically induced gastric cancer in rats can be inhibited by aqueous saffron extracts [36]. In the presence of crocin, adenocarcinoma cells and normal HFSF-P13 cells exhibit an arrest in proliferation, with an increased in BAX levels and a decreased in Bcl-2 mRNA levels [37]. An in vitro study performed by Luo and other researchers investigated the efficacy of crocin and cisplatin alone as well as crocin plus cisplatin. The experiment demonstrated a significant increase in the expression of p53 and BAX following crocin plus cisplatin treatment [38]. Furthermore, there has been reports on inhibiting gastric cancer cell proliferation by treating human gastric cancer cells (BGC-823 cells) with crocetin [37]. Crocetin decreases the mitochondrial membrane potential of BGC-823 cells and promotes cytochrome c translocation. This suggests that crocetin induces apoptosis. In another study, the Bax/Bcl-2 ratio of tumor cells in AGS cells increased due to crocin, thus inhibiting tumor cell growth [39]. The treatment using saffron appears to have a relatively insignificant effect on normal cells. **Table 2** summarizes the findings of several studies using

saffron against gastric cancer.

Table 2. Saffron against gastric cancer

Agent	Cell type or species	Effects	Reference
Crocetin	Rat and AGS cells	Induces apoptosis in AGS cells, acts as an antioxidant, and protects against tissue destruction	Hoshyar R, 2013 ^[37]
Saffron aqueous extract	Rat	Induces inhibition in gastric cancer progression	Luo Y, 2017 ^[38]
Crocetin	BGC-823 cells	Induces apoptosis	Hoshyar R, 2013 ^[37]
Crocin	AGS cells	Induces apoptosis, inhibits tumor cell growth, and has antitumor effect	Li J, 2012 ^[39]

6. Conclusion

Saffron's anti-inflammatory and antitumor properties have been demonstrated in several studies, suggesting that it could be useful for chemoprevention in colorectal cancer. Saffron extracts have been the subject of numerous *in vitro* and *in vivo* studies, but only a few clinical studies have been conducted. Perhaps, this is because saffron is known to have high oral bioavailability and is therefore appropriate for treating gastrointestinal cancers. Saffron is also too costly for pharmaceutical companies to invest in clinical trials. Nevertheless, there are several clinical trials that are now underway.

Disclosure statement

The authors declare no conflict of interest.

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