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Review

Therapeutic potential of saffron, and its chemical components in the treatment of cancers and cardiovascular disorders – a review

Khan, A., *Muhamad, N. A., Taha, R. M., Mohamad, J. and Al-Shara, B.

Institute of Biological Sciences, Faculty of Science, University of Malaya, 50603 Kuala Lumpur, Malaysia

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Abstract

Crocus sativus L., a medicinally important species of the Iridaceae family which produces the herb saffron, plays an effective role in combating various pathogenic disorders including cancers and cardiovascular diseases. Apart from its conventional colorant and aroma-inducing attributes, various phytochemical compounds associated with saffron are now being intensively studied. More than 300 phytochemical compounds, derived from saffron stigmas alone, belong to various classes of secondary metabolites such as carotenoids, terpenoids, flavonoids, and anthocyanins; and they have immense therapeutic applications. Furthermore, pharmacogenomic studies of saffron extracts have revealed promising biocompatible and anticancer potentials against various drug-resistant cell lines which reduce cellular division and proliferation of malignant cells. Keeping in view with the numerous pharmacological properties associated with saffron, the present review explicitly discusses the role of its elemental contents in the prevention and treatment of various cancers and cardiovascular ailments.

Introduction

Crocus sativus L., a perennial stemless herb cultivated as a source of saffron for approximately 4,000 years, belongs to the Iridaceae family (Liliales, Monocots), whose genome size is quite large and poorly characterised (Cardone *et al.,* 2020). Saffron is a dietary spicy plant product collected from three pungent crimson stigmatic lobes of *C. sativus*. At almost €30,000 per kg, saffron is considered as the world's most expensive spice (Pandita, 2021). According to a certain estimate, obtaining 1 kg of dry saffron takes nearly 70,000 – 200,000 flowers, 370 – 470 h of work, and 2,000 m^2 cultivation area (Khan *et al.,* 2020). At present, saffron is mainly grown in Iran, India, Spain, France, Greece, Afghanistan, Azerbaijan, Turkey, and Pakistan; with a global annual production of approximately 418 t per year. Among all these countries, Iran accounts for over 90% of the global saffron production, with 336 t of annual yield, and 90,000 ha of harvest area (Fallahi *et al.,* 2018). Due to cytological impairments such as triploidy and self-incompatibility mechanisms, saffron is generally assumed to be an almost completely sterile triploid crop. Thus, saffron propagates solely through the annual renewal of daughter corms produced by mother corms (Figure 1A).

Saffron is commercially used as spice in foods, and pigment in industries and perfumery. Besides its use in cosmetic preparation and colouring industries, saffron has been used in folk medicine to cure several diseases such as colic, asthma and bronchospasms, insomnia, colds, coughs, cramps, pain, epilepsy, and liver diseases (Cardone *et al.,* 2020). Saffron tea is used as a potential medical/nutritional therapy for the complementary treatment of psoriasis (Hosseinzadeh and Nassiri-Asl, 2013). Many pharmacological reports have demonstrated that this plant and its active compounds possess antimicrobial, antioxidant (Wali *et al.,* 2020), anti-inflammatory, antidepressant, analgesic, anticoagulant (Khan *et al.,* 2020), immunomodulatory (Yousefi *et al.,* 2020), cytotoxic (Shakeri *et al.,* 2020), antitussive (Saadat *et al.,* 2018), and antiplatelet effects (Mohajeri *et al.,* 2020). Traditional and modern biomedical studies have reported that saffron could treat coronary heart diseases (Abedimanesh *et al.,* 2020), respiratory diseases (Boskabady *et al.,* 2020), menstrual disorders (Mohammad *et al.,* 2020), and neurodegenerative disorders (Cardone *et al.,* 2020). These desirable characteristics of saffron could be attributed to its main components: safranal, crocin, picrocrocin, and crocetin. Various non-volatile compounds, of which most of them are carotenoids, such as lycopene, α- and β-carotene, and zeaxanthin play roles in the pharmacological activities of this golden spice (Pandita, 2021). The present review compiles the preventive effects of

*Corresponding author.
Email: nurairina@um.edu.my

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saffron and its principal ingredients, particularly carotenoids, against cancers and cardiovascular diseases (CVDs).

Phytochemical contents

Saffron contains a multitude of phytochemical ingredients associated with various classes of natural substances on the basis of origin, processing conditions, and storage period. The present review summarises the most significant constituents involved in eliciting pharmacological and pharmaceutical activities.

Extensive chemical analysis revealed that saffron stigmas contain more than 300 volatile and non-volatile compounds belonging to different classes of secondary metabolites, including terpenoids, flavonoids, carotenoids, and anthocyanin. Amongst these, carotenoids emerge as the major saffron ingredient, primarily responsible for much of saffron's red colour and aroma (Chahine and Chahine, 2020). Studies have reported the prevalence of lipophilic and hydrophilic carotenoid contents within saffron. Lipophilic carotenoids comprising α- and β-carotene, phytoene, phytofluene, zeaxanthin, and lycopene are found in minor amounts, whilst hydrophilic carotenoids demonstrate relatively increased levels of crocetin and its glycosidic forms digentiobioside (crocin), glucoside, and gentiobioside (Pandita, 2021). Crocetin is a polyene dicarboxylic acid that provides dark red crystals with a melting point of 285°C. Only 6% of crocetin is present in its free form within saffron, and the remaining 94% is present in its glycosidic form. The intense orange-red colour of saffron stigmas is primarily due to the presence of crocetin glycosyl ester, crocin ($C_{44}H_{64}O_{24}$; IUPAC: 8,8-diapo-8,8-carotenoic acid) (Moradi *et al.,* 2020). It constitutes between 6 and 16% of the total dry mass of saffron depending on the cultivating conditions, variety, and processing techniques. Bearing a striking deep red colour, it tends to develop crystals with a melting point of 186°C. Apart from the many species in genus *Crocus*, crocin is also present in *Jacquinia angustifolia, Coleus forskohlii, Buddleja officinalis, Nyctanthes arbortristis*, the fruit and flower of *Gardenia jasminoides*, and *Artocarpus heterophyllus*. Other carotenoids such as β-crocetin, γ-crocetin, and mangicrocin have also been reported in saffron stigmas (Pandita, 2021). Figure 2 shows the chemical structures of the major saffron constituents.

The characteristic of bitter flavour and aroma of saffron are mainly due to the carotenoid oxidation products, picrocrocin, and its de-glycosylated derivate safranal, respectively (Farag *et al.,* 2020).

Figure 1. *Crocus sativus'* corms (A), and flower (B).

Picrocrocin ($C_6H_{26}O_7$), a colourless monoterpene aldehyde, is a degradation product of the zeaxanthin carotenoid responsible for the distinctive bitter taste of saffron (Guclu *et al.,* 2020). Other compounds such as flavonoids also contribute in giving saffron a bitter flavour. The solubility of picrocrocin in water is more than in water-alcohol solutions, but it is totally insoluble in non-polar solutions (Alonso *et al.,* 2001). Picrocrocin, the second most rich constituent by weight, represents 1 - 13% of the dry matter of saffron. Alonso *et al.* (2001) observed the carotenoid contents of saffron from Iran, India, and Spain, and found their picrocrocin content to be 2.18 - 6.15%, 1.07 - 2.16%, and 0.79 - 12.94%, respectively.

The natural de-glycosylation of picrocrocin induces the formation of the volatile aromatic aldehyde safranal ($C_{10}H_{14}O$), which makes up 70% of the total volatile compounds within the plant (Salem *et al.,* 2019). For years, safranal was considered to be the sole aroma-inducing compound in saffron; however, later studies revealed the prevalence of additional volatile compounds playing a pivotal role in generating saffron's distinct aroma. These compounds include 4-ketoisophorone,

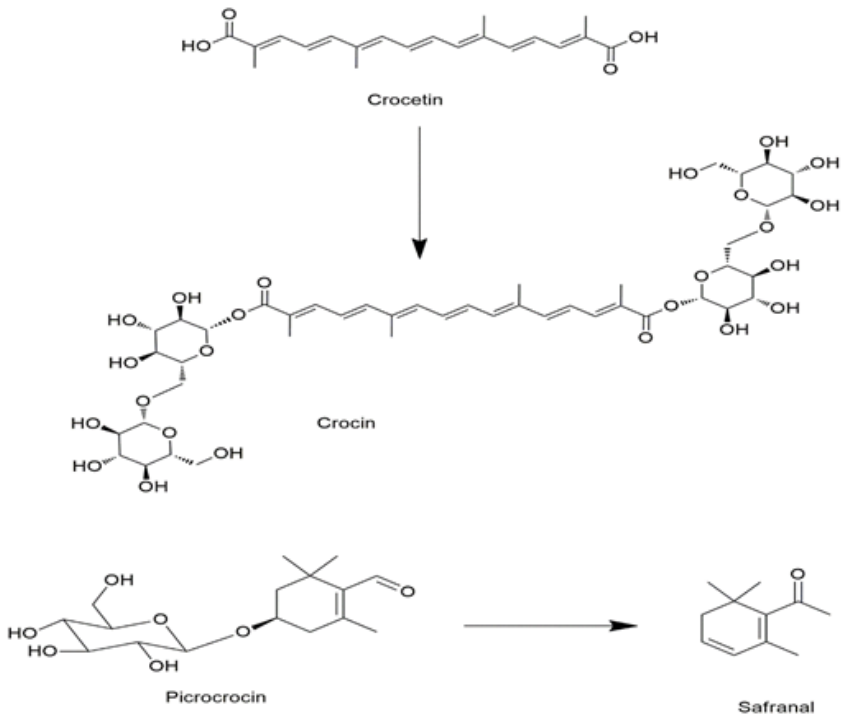

Figure 2. Chemical structures of main constituents of stigma in saffron.

2,6,6-trimethyl-1,4-cyclohexadiene-1-carboxaldehyde, isophorone, 2-hydroxy-4,4,6-trimethyl-2,5-cyclohexadiene-1-one, and 2,2,6-trimethyl-1,4-cyclohexanedione (Pandita, 2021).

Other minor constituents such as terpenoids, flavonoids, anthraquinones, and anthocyanin have also been extracted from stigmas and other parts of saffron plants, mainly petals, pollens, and corms (Gresta *et al.,* 2008). Terpenoids (such as crocusatins) that are found in stigmas and petals of saffron possess a significant anti-tyrosinase activity and amongst the most recovered constituents (Akbar, 2020). Several glycosidic derivatives of terpenoids present in saffron are the precursors of volatile saffron element alternative to picrocrocin. A series of flavonols (glycosidic forms of kaempferol) has also been isolated from the petal and stigma of *C. sativus*; these flavonols, together with picrocrocin, give a distinct bitter taste to saffron (Gahruie *et al.,* 2020). Besides, some phytochemical compounds such as anthocyanin (Alizadeh-Sani *et al.,* 2021) and anthraquinone (Bagri *et al.,* 2017) have been reported to be isolated from petals and corms of *C. sativus*, respectively.

Activities against cancers

Cancer is a serious global public health disorder, claiming more than 9 million lives annually. Approximately, 1.7 million new cases and 0.6 million cancer-related deaths were reported in the U.S. alone in 2019 (Siegel *et al.,* 2019). The prevalence of undesired adverse effects linked to the use of conventional therapeutic techniques such as surgery, chemotherapy, radiotherapy, and immunotherapy, and even recently designated drug therapies mediated against specific cancer targets have compelled researchers to explore alternative treatment approaches. Previous reports have suggested that several dietary compounds such as saffron, ginger, and garlic exhibit promising anticancer and chemo-preventive effects without causing side effects accompanied with the use of synthetic drugs (Mosaddad *et al.,* 2021). Various anticancer properties of saffron and its key ingredients are summarised in Table 1.

Saffron has gained profound interest due to its biocompatible nature and substantial anticancer properties based on various *in vitro* and *in vivo* trials (Hashemi *et al.,* 2020). *In vitro* experiments have shown that amongst various phytochemicals extracted from saffron, crocin has the greatest anticancer potential. Studies carried out as early as 1996 on HeLa cell lines showed that crocin exhibited the greatest cancer inhibitory potential as compared to other phytochemical compounds such as crocetin, picrocrocin, and safranal. The said results were concluded by observing the differences in cellular size, cytoplasmic volume, and other morphological changes, before and after treatment with the compounds (Escribano *et al.,* 1996). Chryssanthi *et al.* (2007) further investigated the antiproliferative property of crocin on two breast cancer cells, MDA-MB-231 and MCF-7, and found that the crocin extracted from any species of *Crocus* is the main

Table 1. A summary of anticancer activities of saffron, and its key components.

Type of cancer	Saffron constituent	Cell line / animal model	Result	Reference
Breast cancer	Crocin and combination of crocin with hyperthermia	MDA-MB-468 cells	Combination of crocin with hyperthermia increased mRNA ratio of Bax/Bcl-2 more than crocin alone.	Mostafavinia *et al.* (2016)
	Crocetin, safranal, and *trans*-crocin-4	MCF-7 and MDA-MB-231 cells	All three constituents suppressed the proliferation of both cell lines, but the antiproliferative activity of saffron was ascribed to crocins regardless of the degree of glycosylation.	Chryssanthi *et al.* (2007)
	Crocin	MCF-7 cells	IC_{50} of crocin was 60 and 12.5 µg/mL at 24 and 48 h.	Lu *et al.* (2015)
	Combination of crocin with paclitaxel or gamma radiation	MCF-7 cells	1.5 - 6 mg/mL crocin inhibited cell growth in a concentration-time dependent manner. The collective effect of crocin with radiation or paclitaxel displayed a synergistic influence on MCF-7 cells.	Vali *et al.* (2015)
	Crocin and crocetin	MCF-7, 4T1 cells, and BALB/c mice	Crocin inhibited SOD activity by scavenging O_2•, whereas crocetin by affecting the copper-binding site. Conversely, both constituents enhanced SOD activity in mice one month after treatment.	Hashemi *et al.* (2020)
	Crocetin β-d-glucosyl ester	MCF-7 and L-6 cells	Inhibition of MCF-7 cells growth without affecting L-6 cells by suppressing oestrogen receptor α/HDAC2-mediated pathway.	Mir *et al.* (2020)
	Crocin and crocetin combination	4T1 cells and BALB/c mice	Crocin and crocetin combination significantly attenuated cell migration, motility, invasion, and adhesion to ECM in 4T1 cells. Mice treated with saffron combination gained weight, enhanced survivability, and reduced tumours.	Arzi *et al.* (2020)
Cervical cancer	Saffron extract, picrocrocin, and crocin	Malignant TC-1 and non-malignant COS-7 cells	IC_{50} values of crocin, picrocrocin, and saffron extract were 1.5, 3 mM, and 4 mg/mL, respectively, confirmed crocin as the main growth inhibiting effect in saffron extract.	Alizadeh and Bolhassani (2015)
	Crocetin	HeLa cells, A549 cells, ovarian cancer SKOV3 cells, and vincristine-resistant breast cancer MCF-7/VCR cells	60 - 240 µmol/L crocetin suppressed cells proliferation dose-dependently by inducing G1 arrest via p53-dependent and -independent pathway assisted with p21WAF1/Cip1.	Zhong *et al.* (2011)
	Saffron ethanolic extract, crocetin, crocin, picrocrocin, and safranal	HeLa cells	IC_{50} values of saffron extract, safranal, picrocrocin, and crocin were 2.3 mg/mL, 0.8, 3, and 3 mM, respectively. Crocetin failed to show cytotoxic activity.	Escribano *et al.* (1996)

	Crocetin	HeLa cells and female Kunming strain mice	Crocetin attenuated COX-2 production in HeLa cells along with plasma MDA, PMN, IL-1, TNF, and nitrates levels in MCA mice.	Chen *et al.* (2015a)
	Saffron ethanolic extract	HEp-2, Vero cells, and Swiss albino male mice	Saffron extract induced dose-dependent cell death of HEp-2 cells. No significant histopathologic differences in the heart, lungs, spleen, kidney, and liver of saffron treated and untreated mice.	Bakshi *et al.* (2016)
Ovarian cancer	Crocin	Ovarian cancer HO-8910 cells	Reduction of cell growth and apoptotic induction by increasing the expression of p53, Fas/APO-1, and Caspase-3.	Xia (2015)
Prostate cancer	Saffron extract and crocin	Human prostate cancer malignant cells LAPC-4, DU145, C4-2B, LnCaP, CWR22, 22rv1, and PC3 non-malignant cells EPN and BPH-1	Both saffron extract and crocin showed a reduction of proliferation in all malignant cells without any cytotoxic effect on non-malignant cells. The expression of Bax was upregulated whereas Bcl-2 was downregulated.	D'Alessandro *et al.* (2013)
	Safranal	PC-3 cells and human foetal lung fibroblast MRC-5 cells	Anti-proliferation of PC-3 cell lines in a concentration- and time-dependent manner. No significant effect of low concentration of safranal after 24 h, however, IC_{50} dose of safranal for PC-3 cells was 13 and 6.4 µg/mL at 48 and 72 h, respectively.	Samarghandian and Shabestari (2013)
	Saffron extract, crocetin, and crocin	Prostate cancer cell lines (PC3 and 22rv1) xenograft athymic male mice	Strongest antitumor activity in PC3 and 22rvl xenografts showed by crocetin compared to saffron extract and crocin. Conversely, saffron extract and crocin induced stronger epithelial differentiation.	Festuccia *et al.* (2014)
Pancreatic cancer	Crocetin	Human pancreatic cancer cell MIA-PaCa-2, BxPC-3, Capan-1 and ASPC-1 xenograft athymic female mice	Apoptosis was significantly stimulated by crocetin in both *in vitro* pancreatic cancer cell lines and *in vivo* athymic mice tumour, as directed by Bax/Bcl-2 ratio.	Dhar *et al.* (2009)
	Crocin	BxPC-3	Apoptotic induction and cell cycle arrest of BxPC-3 cells at G1-phase while reduction of cell viability in a concentration and time-dependent manner.	Bakshi *et al.* (2010)
	Crocin	BXPC-3, Capan-2 cells, Swiss albino mice, and female athymic nude mice	Apoptotic induction and reduction of cell viability of BXPC3 and Capan-2 cells and tumours volume without altering body weight in mice. Also, showed protection against radiation-induced hepatic oxidative stress, reduced liver toxicity, and maintained hepatic morphology.	Bakshi *et al.* (2020)
Colorectal cancer	Saffron extract	Human CRC cells HCT116 (HCT wildtype and HCT p53−/−)	Apoptotic induction and DNA-damage in both cancer cells. Apoptotic induction in HCT116 p53 −/− cells was delayed by autophagy.	Bajbouj *et al.* (2012)
	Saffron extract and crocin	Human CRC cells HCT-116, HT-29, SW-480, human non-small cell lung	Saffron extract and crocin exhibited the most potent antiproliferative activity against HCT-116 cells than the other two cells.	Aung *et al.* (2007)

		cancer cells, and young adult mouse colon cells		
	Crocin	Male ICR mice	Inhibition of azoxymethane/dextran sodium sulphate (AOM/DSS)-induced colitis and DSS-induced colitis in mice by inhibiting cytokines expression.	Kawabata *et al.* (2012)
	Crocin, crocetin, and safranal	SW480 and SW620 cells	Inhibition of cell growth and migration of MACC1 expressing CRC cells by crocin, in a MACC1- and dose-dependent manner via downregulation of DCLK1. Also, reversibly arrested cell cycle progression at G2/M-phase but failed to induce apoptosis.	Güllü *et al.* (2020)
Gastric cancer	Crocetin	Gastric adenocarcinoma AGS cell lines and human normal fibroblast cell line HFSF-PI3; male Wistar albino rats	Inhibition of Bcl-2 and up-regulation of Bax expression in cancer cell lines.	Bathaie *et al.* (2013a)
	Saffron aqueous extract	Male Wistar albino rats	Inhibition of the proliferation of cancer cells dose-dependently.	Bathaie *et al.* (2013b)
	Crocin	Human gastric cancer cell AGS and normal fibroblast HFSF-PI3 cell	2.2 - 3.5 mg/mL crocin improved the cells percentage in the sub-G1 phase up to 60% after 24 h.	Hoshyar *et al.* (2013)
	Crocetin	Human gastric cancer BGC-823 cell	Reduction of mitochondrial membrane potential of crocetin-treated BGC-823 cell lines in a concentration and time-dependent manner.	He *et al.* (2014)
	Crocin	EPG85-257 and EPG85-257RDB cells	Reduction of cell viability of EPG85-257 and EPG85-257RDB cells dose-dependently without affecting MDR1 mRNA expression.	Razavi *et al.* (2020)
	Crocin	Human gastric cancer cells AGS and HGC-27, and normal gastric epithelial cell GES-1	Reduction of KLF5 and HIF-1α, and elevation of miR-320 expression. Upregulation of KLF5 reduced crocin's function and increased HIF-1α expression.	Zhou *et al.* (2019)
Lung cancer	Crocin	A549 and SPC-A1	Suppression of proliferation and apoptotic induction in cancer cell lines dose dependently.	Chen *et al.* (2015b)
	Saffron aqueous extract	A549 and human foetal lung fibroblast MRC-5 cells	IC_{50} of the saffron extract against A549 cells was 380 and 170 µg/mL at 48 and 72 h, respectively.	Samarghandian *et al.* (2013b)
	Crocetin	Male Swiss albino mice	Crocetin scavenged free radicals and increased drug metabolizing enzymes activity.	Magesh *et al.* (2006)
Liver cancer	Saffron ethanolic extract	Liver cancer cell HepG2 and rats	Inhibition of both nodular and foci of altered hepatocytes formation in livers of rats treated with diethylnitrosamine.	Amin *et al.* (2011)
	Crocin	Liver cancer cell line HepG2 and rats	Inhibition of inflammatory markers and reducing the viability of HepG2 cells by arresting cell cycle, apoptotic induction, and downregulating inflammation.	Amin *et al.* (2016)

	Saffron ethanolic extract	Male Wistar rats	Enhancement of GST activity and reduction of MDA level in liver and serum nitric oxide (NO).	Samarghandian *et al.* (2016)
	Crocetin	Male Wistar rats	Protection of hepatic tissue against aflatoxin B_1-induced carcinogenicity.	Wang *et al.* (1991)
	Saffron extract	Liver cancer cell line QGY-7703	Anti-proliferation, apoptotic induction, and G0/G1 phase cell cycle arrest of QGY-7703 cells. Reduction of telomerase activity, level of hTERT, and elevation of Bax/Bcl-2 ratio and P21 expression in QGY-7703 cells.	Liu *et al.* (2020)
	Crocin	Male Sprague Dawley rats	Reduction of experimentally-induced hepatocellular carcinoma through modulating the oxidative/apoptotic pathway. Crocin-induced hepatic expression of Nrf2 improved downstream modifications in KEAP-1 and HO-1 signalling pathway.	Elsherbiny *et al.* (2020)
Skin cancer	Crocin	Female ICR mice	Crocin delayed papilloma's formation in mice .	Konoshima *et al.* (1998)
	Crocetin	Mice fibroblast NIH/3T3 cells	120 and 60 μM crocetin inhibited the activity of TPA-induced protein kinase C by 66 and 50%, respectively.	Wang *et al.* (1996)
	Aqueous saffron extract	Female Swiss albino mice	Saffron treatment before and after DMBA application reduced papilloma formation.	Das *et al.* (2004; 2010)
	Crocin	Human skin cancer cell lines SCL-1 and A431	Anti-proliferation, apoptotic induction, and cell cycle arrest at G0/G1 phase of SCL-1 and A431 cells through Jak2/Stat3 pathway. Downregulation of Bcl-2 expression and elevation of ciprofloxacin, Bid, and procaspase-3 levels.	Wang *et al.* (2018)
Leukaemia	Crocin	Human T-cell leukaemia, MOLT-4 cells	Crocin at higher doses decreased cell viability with elevation in DNA fragmentation of MOLT-4 cells.	Rezaee *et al.* (2013)
	Whole saffron extract, safranal extract, and crocin	Human T lymphocyte, Jurkat cells	IC_{50} values of whole saffron extract and mixture of crocin and safranal against Jurkat cells were 71 and 39 μM, respectively.	Makhloufa *et al.* (2016)
	Crocin, crocetin, and dimethylcrocetin	Promyelocytic leukaemia HL-60 cells	Crocin, crocetin, and dimethylcrocetin inhibited the growth of HL-60 cells with IC_{50} values of 0.8, 2, and 2 μM, respectively.	Tarantilis *et al.* (1994)
	Crocin	Human leukaemia HL-60 cells, male nude BALB/c mice	6.25 and 25 mg/kg crocin showed strong inhibitory effect on HL-60 along with Bcl-2 expression and improved Bax expression in xenografts.	Sun *et al.* (2013)
	Crocin	Human T cells in acute lymphoblastic leukaemia	Proliferation of T cells and cytokine (IL-2 and IL-4) secretion dose dependently, elevation of CD4/CD8 ratio of T cells with no significant damage, and reduction of DNA damage in cytarabine-treated T cells.	Zhang *et al.* (2018)

constituent responsible for antiproliferation, regardless of the degree of glycosylation. This finding was also supported by Nasimian *et al.* (2020). A recent report revealed that crocetin β-D-glucosyl ester restrained the proliferation of MCF-7 cell lines without significantly affecting normal muscle cell line (L-6) by suppressing the oestrogen receptor α/HDAC2-mediated signal pathway (Mir *et al.,* 2020). An *in vivo* mouse model of breast cancer showed that the administration of crocin and crocetin increased the superoxide dismutase (SOD) activity one month after treatment. In contrast to the *in vivo* results, crocin and crocetin restricted the SOD activity *in vitro* and in MCF-7 breast cancer cells. Crocin inhibited the SOD activity by scavenging superoxide radical (O_2•), whereas crocetin inhibited SOD by affecting the copper-binding site (Hashemi *et al.,* 2020). In another experiment, treatment of triple-negative breast cancer, 4T1 cells, with a combination of crocin and crocetin significantly attenuated cell migration, motility, and invasion; and reduced adhesion to the extracellular matrix. Furthermore, mice treated with saffron combination demonstrated weight gain, enhanced survivability, and reduced tumours (Arzi *et al.,* 2020).

Cervical cancer (CC) is the fourth most leading cause of cancer-related deaths amongst women throughout the world, accounting for nearly 0.53 million new cases and 0.27 million mortality annually (Gaffney *et al.,* 2018). High-risk human papillomavirus infection, childbirth, the use of oral contraception, smoking, age, and diet are some of the major risk factors commonly linked with developing CC (Olusola *et al.,* 2019). CC development is asymptomatic in its early stages. Therefore, early detection and treatment of precancerous cervical lesions is important to timely diagnose and minimise CC prevalence. Several data reported that saffron reduced the colony formation and DNA and RNA syntheses in HeLa cervical epithelioid carcinoma cell lines (Escribano *et al.,* 1996). Crocetin showed an antiproliferative effect in HeLa cell lines in a dose-dependent manner through the activation of p53 and p21 pathways, and its combined effect with vincristine significantly improved the anticancer efficacy of vincristine (Zhong *et al.,* 2011). In an *in vivo* study, crocetin supplementation attenuated plasma MDA, PMN, IL-1, TNF, and nitrate levels in methylcholanthrene-induced mice. Furthermore, crocetin inhibited cyclooxygenase-2 production in HeLa cell lines (Chen *et al.,* 2015a). Likewise, saffron extract induced dose-dependent cell death of HEp-2 cells, and exhibited no significant histopathologic differences in the heart, lungs, spleen, kidney, and liver of saffron-treated (300 mg/kg of body weight) and untreated mice (Bakshi *et al.,* 2016). These studies suggested that saffron constituents, particularly crocin and crocetin, have the potential to be used as effective therapeutic agents against CC.

D'Alessandro *et al.* (2013) evaluated the inhibitory potential of crocin and saffron extracts on five malignant and two non-malignant cells. The results indicated that both test compounds decreased the proliferation of all malignant cells with no observable cytotoxic effects in non-malignant cells. Flow cytometry analysis indicated that most of the cells were arrested at the G_0/G_1 phase, with a notable existence of apoptotic cells. Western blot analysis showed that the expression of Bax, a pro-apoptotic protein, was upregulated; whereas that of Bcl-2, an anti-apoptotic protein, was strikingly downregulated. Moreover, a study of the enzymatic activity of caspase showed a caspase-dependent pathway with high levels of caspase-9, suggesting the activation of mitochondrial associated apoptosis (intrinsic mitochondria pathway). Similarly, a preclinical research reported by Samarghandian and Shabestari (2013a) revealed significant concentration-dependent cytotoxic effects of safranal against human prostatic carcinoma cell (PC-3) when compared with non-malignant cells. Further, *in vivo* results revealed the strongest antitumour activity by crocetin when compared with saffron extract and crocin in PC3 and 22rvl xenografts. Conversely, saffron extract and crocin induced stronger epithelial differentiation. In addition, saffron extract and its constituents suppressed PCa cell migration and invasion via downregulation of metalloproteinase and urokinase activity, thus suggesting that these chemotherapeutic compounds may have a promoting influence on metastasis (Festuccia *et al.,* 2014). On the basis of these observations, saffron could be applied as a promising chemotherapeutic drug for prostate cancer.

Pancreatic cancer has the seventh-highest rate of mortality amongst patients with cancer, having an average survival of six months and a dismal five-year survival frequency of around 8% (Aier *et al.,* 2019). The mortality rate of pancreatic cancer is rapidly increasing worldwide, and is expected to become the second most common cause of all malignant tumours by 2030 (Zhu *et al.,* 2018). Therefore, new therapeutic alternatives are intensely required for people suffering from pancreatic adenocarcinoma. During the last few years, a series of experiments has been carried out *in vitro* and *in vivo* to elucidate the influence of saffron constituents on the growth and proliferation of pancreatic cancers

(Bakshi *et al.,* 2020). Dhar *et al.* (2009) demonstrated the anti-tumorigenic activity of crocetin against pancreatic cancer by using human pancreatic cancer cells such as Capan-1, ASPC-1, MIA-PaCa-2, BxPC3, and a xenograft athymic mouse model. The results revealed that crocetin suppressed the proliferation of pancreatic cancer cells, and significantly reduced cell distribution within the S-phase, thus confirming the impairment in DNA replication. Crocetin significantly altered cell cycle regulatory proteins such as Cyclin-B1, Cdc-25C, Cdc-2, and epidermal growth factor receptor (EGFR). In an *in vivo* study, MIA-PaCa-2 cell lines were directly injected into xenograft athymic mice, followed by oral treatment of crocetin after palpable tumour development. The findings indicated a significant rise in proliferating cell nuclear antigen-positive cells in the control samples when compared with the crocetin-treated samples. In addition, a significant decrease in EGFR expression and phosphorylation was observed in mice treated with crocetin when compared with the untreated samples (Dhar *et al.,* 2009). Bakshi *et al.* (2010) examined the anticancer properties of crocin on human pancreatic cancer cells Bx-PC-3, and found that crocin induced cell proliferation, the development of cell apoptosis, and G1-phase cell cycle arrest of BxPC-3 cells. The authors further investigated the effect by using an *in vivo* mouse model, showing that crocin significantly reduced tumour volume without altering body weight. In addition, it offered protection against radiation-induced hepatic oxidative stress, attenuated the levels of liver toxicity, and maintained hepatic morphology (Bakshi *et al.,* 2020). These findings showed that crocetin has an effective anti-tumorigenic efficacy against pancreatic cancers *in vitro* and *in vivo*.

Colorectal cancer (CRC), the third most commonly caused malignancy, accounts for 6.1% of all cancer incident globally, with approximately 1.8 million new cases diagnosed annually (Bray *et al.,* 2018). New therapeutic strategies have been developed in the last few decades due to the increase in knowledge of the molecular biology of the disease. Aung *et al.* (2007) examined the antiproliferative assay of crocin and saffron extract on CRC cells such as HT-29, HCT-116, and SW-480, and suggested that these two constituents significantly suppressed the proliferation of cancer cell lines without any harm to normal cells. A similar experiment by Bajbouj *et al.* (2012) determined that saffron extract was effective in apoptotic induction in CRC cells. They treated HCT116 human colon cancer cells (HCT p53−/− and HCT wild type) with a saffron extract, and the treatment resulted in DNA damage and apoptotic cell death in both cancer cell lines. The expression of metastasis-associated colon cancer 1 (MACC1) oncogene has been clinically shown to promote tumour progression and migration in as many as 20 different solid tumour types, including CRC (Radhakrishnan *et al.,* 2018). In an attempt to explore the antiproliferative effect of saffron on MACC1-induced cancer cell proliferation and motility, Güllü *et al.* (2020) reported that saffron crudes, particularly crocin, inhibited cell growth and the migration rate of MACC1 expressing CRC cell lines in a MACC1- and concentration-dependent manner through the downregulation of the cancer stem cell marker DCLK1. Saffron reversibly arrested cell cycle progression at the G2/M-phase, but failed to induce apoptosis. Therefore, saffron should be examined further in detail as a viable drug in preventing the development of CRC.

Recent studies have unveiled the influence of saffron and its chemical components to combat the risks associated with gastric cancer (Naeimi *et al.,* 2019). Crocin restricted cell viability in a dose-dependent manner, with higher intensity on human EPG85-257 cells than in EPG85-257RDB gastric cancer cell lines. However, it showed no significant changes in the expression of *MDR1*. Conversely, crocin enhanced the cytotoxicity of doxorubicin in EPG85-257 and EPG85-257RDB cell lines, and this enhancement may be induced by the reduced expression of *MDR1* (Razavi *et al.,* 2020). Similarly, crocin reduced the expression of KLF5 and HIF-1α, and enhanced that of miR-320. Upregulation of KLF5 significantly reduced crocin's function and increased the expression of HIF-1α, indicating that crocin suppresses the EMT, invasion, and mobility by attenuating the expression of KLF5 in gastric cancer cell lines (Zhou *et al.,* 2019). An *in vivo* study of Bathaie *et al.* (2013a) indicated that aqueous saffron extract has beneficial effects on 1-methyl-3-nitro-1-nitrosoguanidine-induced gastric cancer in rats. Pathologic data indicated that saffron extract administration inhibited cancer progression in the gastric tissue, in such a way that 20% of cancer-bearing rats administered with a higher concentration of saffron extract were found to be totally normal after clinical trials. Furthermore, the apoptosis/proliferation rate enhanced with the treatment of saffron extract in cancerous rats as indicated by flow cytometry analysis/propidium iodide staining (Bathaie *et al.,* 2013b). Thus, pharmacologists recommend saffron and its extract as a potential chemotherapeutic agent against gastric cancer.

The aqueous and ethanolic extract of saffron is also known to play a vital role as a tumoricidal agent in lung cancer, the most commonly diagnosed (11.6%) and leading cause of cancer-associated mortality (18.4%) worldwide (Bray *et al.,* 2018). Samarghandian *et al.* (2010) proved that the administration of ethanolic extract of saffron significantly suppressed the growth of A549 cells in a concentration- and time-dependent manner, when compared with non-malignant (L929) cells to determine the cytotoxic and antiproliferative potential of saffron in carcinomic human alveolar basal epithelial cells (A549). A similar study of Samarghandian *et al.* (2013b) reported that the proliferation of A549 malignant cells significantly attenuated following treatment with aqueous extract of saffron in a dose- and time-dependent manner. Furthermore, the frequency of apoptotic cells was improved. This study strongly suggested that the aqueous and ethanolic extracts of saffron could be used as a promising chemo-preventive drug for lung cancer (Samarghandian *et al.,* 2010; 2013b).

The chemoprevention of hepatocellular carcinoma (HCC), the second most frequent cause of cancer-related deaths amongst males, is a promising approach against its development and metastasis (Bray *et al.,* 2018). Natural herbs and plants, such as saffron, have received immense attention for their role as an antiproliferative and proapoptotic agent in different hepatocellular cancer cell lines (Sumaiya *et al.,* 2020). Saffron treatment significantly restricted cell growth and induced cell apoptosis, and the G0/G1 phase cell cycle arrest QGY-7703 cell lines. Furthermore, saffron decreased the telomerase activity and the level of hTERT, and increased Bax/Bcl-2 ratio and the expression of P21 in QGY-7703 cell lines (Liu *et al.,* 2020). In a study by Amin *et al.* (2011), saffron administration to diethylnitrosamine (DEN)-treated rats significantly decreased the number and frequency of hepatic dyschromatic nodules and development of the foci of altered hepatocyte. Treatment with saffron also resulted in counteracted DEN-induced oxidative stress in an animal model, as shown by the reestablishment of antioxidant enzymes such as catalase (CAT), SOD, and glutathione-S-transferase (GST) levels, and the lowering of malondialdehyde (MDA), myeloperoxidase activity, and protein carbonyl production in liver. Amin *et al.* (2016) further studied the anti-tumorigenic activity of crocin in HCC by using human liver cancer cell lines (HepG2). Their findings showed the antiproliferative and pro-apoptotic characteristics of crocin when administrated in HCC-induced rats. Recently, crocin administration reduced experimentally induced hepatocellular carcinoma by modulating the oxidative/apoptotic pathway. The crocin-induced hepatic expression of Nrf2 promoted downstream modifications in the endogenous KEAP-1 and HO-1 signalling pathway that regulates various apoptotic modulators such as Bcl-2, Bax, caspase-8, TRAIL, p53, and cJNK (Elsherbiny *et al.,* 2020). These results showed that saffron, in combination with other commonly used chemotherapeutic drugs, could be used against liver cancer.

Over the past several decades, pharmacists have become interested in understanding the cellular and molecular mechanisms of skin cancer, and discovered substances to be used in its chemoprevention (Paulson *et al.,* 2019). Fortunately, these days, the chemoprevention of cancer is known to be the most hopeful and innovative strategy to suppress or inverse the tumorigenesis process by using different natural products or plants. *In vitro* findings have reported that crocin could slow down the development of mouse skin papillomas when compared with other saffron-tested carotenoid pigments such as crocetin gentiobiose glucose ester and crocetin di-glucose ester (Konoshima *et al.,* 1998). Likewise, crocin inhibited the proliferation and cell cycle arrest at the G0/G1 phase, and induced cell death in SCL-1 and A431 skin cell lines through the Jak2/Stat3 pathway. It also downregulated the expression of Bcl-2 and elevated the ciprofloxacin, Bid, and procaspase-3 levels in crocin-treated cells (Wang *et al.,* 2018). The chemo-preventive potential of aqueous saffron extract on two-stage skin carcinogenesis in albino mice starting with 7,12 dimethylbenz[a]anthracene and followed by croton oil was assessed. Standard histological analysis of the skin revealed significant suppression in papilloma formation when saffron was administered before and after the induction of skin papillogenesis. The suppression of skin papillogenesis could be attributed to the modulatory activities of saffron on phase II detoxifying enzymes, namely, glutathione peroxidase (GPx), SOD, CAT, and GST (Das *et al.,* 2004; 2010). Further research is required to examine the mode of action of saffron and make it a potential therapeutic agent against skin cancer.

Numerous experiments have illustrated that saffron and its characteristic components inhibit the proliferation and carcinogenicity of leukemic cells. According to Rezaee *et al.* (2013), a significant reduction in growth and viability of human T-cell leukaemia cells MOLT-4, and an increase in DNA fragmentation was recorded at higher doses of crocin treatment. The mild cytotoxic activities of crocin on

MOLT-4 may be mediated by DNA fragmentation. *In vitro* curative experiments have proven that crocin suppressed the proliferation of human leukaemia HL-60 cell line, and promoted apoptosis and cell cycle arrest at the G0/G1 phase in concentration- and time-dependent manners (Sun *et al.,* 2013). Likewise, crocin induced the proliferation of T cells and cytokine (IL-2 and IL-4) secretion in a dose-dependent manner. It also enhanced the CD4/CD8 ratio of T cells, with no significant damage, but reduced DNA damage in cytarabine-treated T cells (Zhang *et al.,* 2018). A nude mouse xenograft model was used to assess the *in vivo* effect of crocin on human leukaemia, and the results demonstrated that crocin suppressed the tumour weight and size of HL-60 cells in the mouse model. Moreover, it inhibited the expression of Bcl-2 and improved that of Bax in xenografts (Sun *et al.,* 2013). Makhloufa *et al.* (2016) further tested the antiproliferative effect of Lebanese saffron on human acute lymphoblastic T-cell leukaemia (Jurkat cells), and found that saffron extract and a mixture of its components (safranal and crocin) reduced the proliferation of Jurkat cells in a dose-dependent manner. However, the IC_{50} value of the whole saffron extract was higher than that of its mixture. These findings suggested that saffron and its characteristic components could be used as a viable option against leukaemia in clinical trials.

Activities against cardiovascular diseases

CVDs are major threats to global health, claiming nearly 17.8 million lives globally in 2017, which corresponds to 330 million years of life lost and another 35.6 million years lost due to disability (Roth *et al.,* 2018). The number of CVD deaths globally increased from 12.3 million (25.8%) in 1990 to 17.8 million (31.5%) in 2017, and it is expected to cross 22.2 million by 2030 (Sahin and Ilgun, 2020). Apart from the high level of death rates due to CVDs, they also cause suffering within families through decreasing their quality of lives at the micro-level, and they cause serious fiscal implications with respect to health expenditure of countries at the macro-level. In particular, low and low-middle income countries have been adversely affected by CVDs. In 2015, for example, 82% of global non-communicable disease deaths occurred in low and middle-income countries, with 37% of such deaths were attributed to CVDs (Roth *et al.,* 2018; Sahin and Ilgun, 2020). The high mortality rate of CVDs highlights the need for an effective treatment approach. Recent experiments have shown several therapeutic properties of saffron in the effective treatment of many cardiovascular-related disorders including atherosclerosis, hyperlipidaemia, and several others (Razavi and Hosseinzadeh, 2020), and are summarised in Table 2.

The anti-atherosclerotic activity of saffron and its chemical components have been documented in various *in vitro* and *in vivo* studies. Liu and Qian (2005) evaluated the preventive effect of crocin on cholestane-3β, 5α, 6β-triol-induced apoptosis, along with the gene expression patterns of cultured endothelial cells. They found that crocin inhibited the apoptosis of endothelial cells by improving the expression of Bcl-2, and decreasing that of Bax and Caspase-3. Further studies confirmed that the antiapoptotic property of crocin plays a key role in the prevention and regression of atherosclerosis (Xu *et al.,* 2007). Crocetin and crocin also caused anti-atherosclerotic effects in quail by reducing the level of ox-low-density lipoprotein (LDL) that induces gene expression in endothelial cells, thereby resulting in the progression of atherosclerosis (He *et al.,* 2005; 2007). Besides, crocetin attenuated high cholesterol diet-induced dyslipidaemia in rats, potentially due to the anti-inflammatory, antioxidative, and downregulating effects of phosphorylated-p38 MAPK efficacy by this saffron constituent (Diao *et al.,* 2018). Recently, in a double-blinded, placebo-controlled clinical trial, crocin enhanced the expression of *AMPK* and *SIRT1*, and attenuated that of *NF-κB* and *LOX1* in the peripheral blood mononuclear cells of patients with coronary artery disease. Furthermore, the administration of crocin decreased the levels of serum ox-LDL and *MCP-1*, and improved anthropometric variables (Abedimanesh *et al.,* 2020).

High levels of lipids are considered as a primary factor involved in the development of CVDs. Pharmacologists are currently focusing on novel drugs with the capability to reduce and regulate cholesterol and the triglyceride (TG) content of serum. Sheng *et al.* (2006) examined the hypolipidemic property of crocin extracted from *G. jasminoides* Ellis in rats, and indicated that the compound significantly reduced the serum TG, total cholesterol, LDL cholesterol, and very LDL cholesterol level in rats. The authors added that the hypolipidemic activity of crocin was attributed to its suppression of pancreatic lipase activity. Similar findings were obtained by Lee *et al.* (2005), where the crocetin and crocin isolated from *G. jasminoides* improved hyperlipidaemia. Furthermore, the mean plasma MDA level, lipid profile, SOD enzyme activity of RBCs, and inflammatory markers were elevated in rats administered with saffron petal

Table 2. A summary of anti- cardiovascular disease activities of saffron, and its key components.

Cardiovascular disease	Saffron constituent	Cell line / animal model	Result	Reference
Atherosclerosis	Crocin	Human endothelial cell	Elevation of Bcl-2 expression and reduction of Bax gene expression and Caspase-3 activity.	Liu and Qian (2005)
	Crocin (from *G. jasminoides*)	Bovine aortic endothelial cells, bovine aortic smooth muscle cells, and male quails	9-week treatment with crocin lessened Ox-LDL level that induces gene expression in endothelial cells thus suppressed atherosclerosis production in quails.	He *et al.* (2005)
	Crocetin (from *G. jasminoides*)	Male quails	9-week treatment with crocetin lessened serum triglycerides (TG), total and LDL cholesterol levels, and suppressed aortic plaque development along with reducing malonaldehyde and thwarted decreased level of serum nitric oxide.	He *et al.* (2007)
	Crocetin	Swiss Albino Wistar rats	Attenuation of HCD-induced dyslipidaemia in rats.	Diao *et al.* (2018)
	Saffron aqueous extract and crocin	Placebo-controlled, randomised clinical study in CAD patients	Elevation of *AMPK* and *SIRT1* expression, attenuation of *NF*-κB and *LOX1* expression in crocin group. Also, crocin supplementation decreased levels of serum ox-LDL and *MCP-1* and improved anthropometric variables.	Abedimanesh *et al.* (2020)
Hyperlipidaemia	Crocin (from *G. jasminoides*)	Male Sprague Dawley rats	10-day treatment with crocin decreased serum TG, total, and LDL cholesterol as well as very low-density lipoprotein (VLDL) cholesterol level.	Sheng *et al.* (2006)
	Crocetin and crocin (from *G. jasminoides*)	Male ICR mice	Both crocetin and crocin suppressed serum TG, total, LDL, and VLDL cholesterol level.	Lee *et al.* (2005)
	Saffron and crocin	Albino Wistar rats	High saffron dose showed more effectiveness in counteracting the manifestation of hyperlipidaemia than high crocin dose.	Asdaq and Inamdar (2010)
	Saffron aqueous extract	Male Albino Wistar rats	Saffron extract dose dependently decreased serum TG, LDL, total lipids, and cholesterol level but increased serum HDL level.	Samarghandian *et al.* (2014)
	Saffron petal hydroalcoholic extract	Male Wistar rats	Elevation of lipid profile, SOD, MDA levels, and inflammatory markers in saffron treated rats, despite receiving high-cholesterol diet.	Mohamadpour *et al.* (2020)

Hyperglycaemia	Crocin	Neonatal male Wistar rats	9-week treatment with crocin lessened serum glucose, total and LDL cholesterol, TG, advanced glycation end products levels, and improved HDL in diabetic rats.	Shirali *et al.* (2013)
	Safranal	Albino Wistar rats	Safranal dose-dependently decreased blood glucose, MDA, TG, NO, total lipids and cholesterol, and increased GSH level as well as CAT and SOD activity.	Samarghandian *et al.* (2013a)
	Saffron aqueous extract	Male Albino Wistar rats	Elevation of body weight and serum TNF-α but reduction in blood glucose level and serum advanced glycation end products levels along with glycosylated serum proteins.	Samarghandian *et al.* (2014)
	Saffron methanolic extract, safranal, and crocin	Male adult Wistar rats	Reduction in blood glucose and HbA1c concentration but elevation in the insulin content of blood with no significant effects on blood SGPT, SGOT, and creatinine concentration.	Kianbakht and Hajiaghaee (2011)
	Crocetin (from *G. jasminoides*)	Male Wistar rats	Crocetin thwarted dexamethasone-induced insulin resistant and enhanced insulin sensitivity in rats fed fructose by regularising protein and mRNA expression of TNF-α, adiponectin, and leptinin epididymal white adipose tissue.	Xi *et al.* (2005; 2007)
	Crocin	Female Wistar rats	Treatment with crocin ameliorated histopathological damages in heart tissue and decreased the level of MDA, TG, total and VLDL cholesterol levels, accompanied by an increase in GSH contents of both serum and heart tissue.	Altinoz *et al.* (2015)
	Crocin	Zebrafish	Reduction in glucose levels and elevation of insulin and pck1 expression in zebrafish larvae.	Kakouri *et al.* (2020)
	Saffron dried extract	Randomised double-blinded clinical study in T2D patients	Reduction in cholesterol, HbA1c, FPG, LDL-c, and LDL/HDL ratio.	Aleali *et al.* (2019)
Anti-hypertension	Saffron extract, safranal, and crocin	Male Wistar rats	Saffron extract and constituents' dose-dependently decreased MAP in hypertensive and normotensive rats.	Imenshahidi *et al.* (2010)
	Saffron aqueous extract	Adult male Wistar rats	Saffron extract dose-dependently decreased mean SBP in desoxycorticosterone acetate (DOCA)-salt induced hypertensive rats.	Imenshahidi *et al.* (2013)
	Saffron hydroalcoholic extract	Male Wistar rats	Saffron extract prevented BP elevation, decreased aortic cross-sectional area, tunica media thickness, and number of elastic lamellae in hypertensive rats.	Nasiri *et al.* (2015)

	Saffron stamen hydroalcoholic extract	Male Wistar rats	No significant changes in basal cardiovascular parameters. Also, attenuation of the pressor effect induced by Ang 2, high MAP, and SBP induced by L-NAME and improvement in BRS.	Reza *et al.* (2020)
	Saffron powder	Placebo-controlled, double-blind, randomised clinical study in T2D patients	Attenuation of SBP in T2D patients without showing any significant effect on DBP, liver functions, and nephropathy indices.	Ebrahimi *et al.* (2019)
Myocardial ischemia	Crocetin and crocin	Male Sprague Dawley rats	Orally administered crocetin protected the injured myocardial cell both *in vitro* and *in vivo* in comparison with crocin.	Zhang *et al.* (2009)
	Crocetin ester	Sprague Dawley rats	Treatment with crocetin ester exerted cardioprotection against ISO-induced acute myocardial ischemia by Rho/ROCK/*NF*-κ*B* signalling pathway.	Huang *et al.* (2016)
	Saffron extract	Rat embryonic ventricular cardiomyocyte cell line H9c2	Saffron extract activated the levels of phosphorylated AKT, 70S6 kinase, and ERK1/2, recovered contractile proteins expression, inhibited alteration in mitochondrial morphology, and reduced caspase-3 activity in H9c2 cardiomyocytes.	Chahine *et al.* (2016)
	Safranal	Male Sprague Dawley rats	Reduction of serum CK, LDH, MDA, and intracellular Ca^{2+} concentration, and elevation of serum SOD and ROS production. Also, improved changes in heart morphology and inhibited contraction, Ca^{2+} transients, and $I_{Ca\text{-}L}$ in isolated ventricular myocytes.	Xue *et al.* (2020)
	Crocetin	Sprague Dawley rats	Elevation of left ventricular SBP, +dp/dt max and -dp/dt max, myocardial Bcl-2/Bax and p-Akt/Akt ratio, myocardial GPx, SOD levels, reduction of left ventricular end DBP, myocardial infarct size, CK-MB, serum LDH, cardiac troponin I, MDA, TNF-α, interleukin-1β, and interleukin-6 levels.	Liu *et al.* (2019)

hydroalcoholic extract when compared with the control group, despite receiving high-cholesterol diet (Mohamadpour *et al.,* 2020). In further studies, saffron was reported to be more effective in responding to hyperlipidaemia manifestation than crocin, thus suggesting the involvement of another active saffron component other than crocin in the synergistic antihyperlipidemic and antioxidant activity of saffron (Asdaq and Inamdar, 2010).

Hypertension has long been known as one of the most serious risk factors for CVDs and mortality. Globally, 31.1% (1.38 billion) of the adult population was living with hypertension in 2010, and the prevalence of hypertension is predicted to increase to 1.56 billion by 2025 (Cao *et al.,* 2019). Over the past two decades, studies have shown that most people living in developing countries experience increased incidences of hypertension. Therefore, the detection of hypertension and its control is critically important to overcome the possible risk of heart attacks and strokes. Many traditional medicinal plants, including saffron, have been globally reported to be antihypertensive (Singh *et al.,* 2020). An *in vivo* study comparing the hypotensive activity of aqueous extract of saffron and the compounds crocin and safranal against normotensive and desoxycorticosterone acetate-induced hypertensive rats revealed that the saffron extract and compounds reduced the MABP of rats in a dose-dependent manner. The authors further suggested safranal as the principal constituent eliciting the antihypertensive effect of the saffron extract (Imenshahidi *et al.,* 2010). Similarly, treatment with aqueous extract of saffron significantly decreased MSBP in DOCA-salt-induced hypertensive rats in a dose-dependent manner. However, the hypotensive activity of saffron extract did not persist as the systolic blood pressure (SBP) started to increase after stopping the saffron administration (Imenshahidi *et al.,* 2013). Recently, saffron stamen extract showed no significant changes in the basal cardiovascular parameters. However, it reduced the pressor effect induced by angiotensin 2 (Ang 2), high mean arterial pressure, and L-NAME-induced SBP, and improved the baroreflex sensitivity in a rat model (Reza *et al.,* 2020). Similarly, in a 12-week double-blind, randomised clinical study, saffron powder supplementation improved SBP in patients with type 2 diabetes mellitus (DM) without showing any significant effect on diastolic blood pressure (DBP) when compared with the placebo (Ebrahimi *et al.,* 2019). These findings supported further investigations of saffron and its constituents in clinical settings for the potential treatment of hypertension.

DM, a chronic disorder characterised by high blood pressure with alteration in carbohydrate, protein, and fat metabolisms, is one of the major factors affecting the renal, retinal, and nervous systems (Eslami *et al.,* 2020). In addition, it is closely associated with hyperlipidaemia and hypertension, that both result in cardiovascular morbidity and mortality. The global DM prevalence amongst adults increased from 108 million in 1980 to 463 million in 2019. Various estimates suggested that the global prevalence of DM could escalate to 578 million by 2030 and 642 million by 2040 (Saeedi *et al.,* 2019). Recent reports showed the possible inhibitory effect of saffron against DM complications such as oxidative stress, hyperglycaemia, and hyperlipidaemia (Razavi and Hosseinzadeh, 2020). Safranal administration after streptozotocin (STZ) treatment significantly decreased the blood glucose level, nitric oxide, serum malondialdehyde (MDA), total lipids, TGs, and the cholesterol level, with elevation in the glutathione (GSH), CAT, and SD activity levels in safranal-treated diabetic rats (Samarghandian *et al.,* 2013a). Another experiment by the same team revealed that saffron extract significantly improved the GSH, CAT, and SD activities; significantly reduced serum TNF-α and cognitive deficit; and promoted the activity of nitric oxide synthase in the hippocampal tissue of diabetic rats. As a result, saffron reduced the possible risk of hyperlipidaemia, hyperglycaemia, and oxidative stress in diabetic rats (Samarghandian *et al.,* 2014). Crocin administration after STZ treatment enhanced histopathological changes in heart tissue and reduced the MDA levels, with elevation in GSH levels of the serum and heart tissue (Altinoz *et al.,* 2015). In a recent study, crocin supplementation showed a reduction in glucose levels and an elevation in the expression of insulin and phosphoenolpyruvate carboxykinase 1 (pck1) in zebrafish larvae, thus showing the key role of saffron constituents in insulin management and glucose metabolism (Kakouri *et al.,* 2020). Likewise, in a randomised, double-blinded clinical study, three-month application of crocin significantly reduced cholesterol, glycated haemoglobin, fasting plasma glucose, LDL-c, and the LDL/HDL ratio when compared with placebo (Aleali *et al.,* 2019). Overall, these findings showed that saffron and its active constituents may inhibit DM-induced CVD by modulating oxidative stress, hyperglycaemia, and dyslipidaemia.

Myocardial ischemia, which is caused by critical coronary artery obstruction, is one of the most common coronary heart diseases that result in increased morbidity and mortality worldwide,

especially in the Western world. Several natural products, including saffron, have been tested for their activity against cardiac ischaemia (Chahine and Chahine, 2020). An *in vivo* rat model of myocardial injury revealed that crocetin reduced the secretion of lactate dehydrogenase (LDH), creatine kinase (CK), and MDA levels, and enhanced the SOD level and cardiac myocyte activity in rats. However, serum-containing crocin showed no remarkable improvement in myocardial injury. The authors remarked that crocin is barely absorbed through the gastrointestinal tract following oral administration, and its quantity in serum is very low (Zhang *et al.,* 2009). Xue *et al.* (2020) further investigated the anti-myocardial ischaemic effects of safranal, and showed that it improved changes in cardiac morphology, with a significant preventive effect on myocardial ischaemia induced by isoproterenol (ISO), and acted as a Ca^{2+} channel antagonist. The cardioprotective role of safranal is related to the regulation of Ca^{2+} homeostasis and antioxidative stress. In an attempt to investigate the preventive effect of saffron on the myocardial ischaemia-reperfusion injury, Liu *et al.* (2019) reported that crocetin significantly increased the left ventricular SBP, +dp/dt max and -dp/dt max, myocardial Bcl-2/Bax and p-Akt/Akt ratio, and myocardial SOD and GPx levels; and attenuated the left ventricular end DBP, myocardial infarct size, CK-MB, serum LDH, cardiac troponin I, MDA, TNF-α, IL-1β, and IL-6 levels. Similarly, Huang *et al.* (2016) reported the efficacy of crocetin ester in the reduction of serum contents of pro-inflammatory cytokines, along with CK, MDA, LDH, and SOD activities. Crocetin ester also ameliorated the histopathological alteration. The authors assumed that ISO-induced acute myocardial ischaemia could be possibly treated by crocetin ester *via* the suppression of the Rho/ROCK/*NF-κB* pathway.

Conclusion

In conclusion, as the world population increases, the number of cases related to cancers and CVDs are also increasing and causing mortality in masses throughout the world. In such challenging situation, saffron, a multipotential drug, has been recognised to have the ability to inhibit and decrease the risk of major chronic diseases, including cancers and CVDs. Although experimental studies showed promising results, clinical trials are still rare, and more in-depth studies and laboratory research with special emphasis on clinical trials in humans are needed.

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