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Review article

Phytochemical analysis and antioxidant activities of *Crocus sativus*, a comprehensive and updated review based on experimental and clinical studies

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Abstract

Objective: The antioxidant power of *crocus sativus* (Cs) makes it a desirable natural medicine in the cases of not only treating but also preventing different diseases. This article furnishes a critical and current review of the experimental and clinical studies concerning phytochemical analysis and antioxidant properties of Cs, which have the potential of development of new therapeutic intervention to the disorder, to prevent or treat conditions related to oxidative stress and inflammation.

Materials and Methods: The literature on antioxidant effects of Cs published between 2003 and the end of October 2025 was searched on database like PubMed, WOS, Science direct and Scopus. **Results:** The *in vitro* experiments showed that the plant hold great protection against the oxidative stress-related damage to cells. Their physiological effects have been tested *in vivo*, where there is an improvement in disease models.

The anti-oxidant effectiveness of the plant conducted in clinical trials indicated that Cs exhibits antioxidant effects as its major mechanism of action. These reviews have shown that Cs is instrumental in its role in therapeutic solutions of multiple pathologies. Along with summarizing the current knowledge, this review also reveals the importance of additional studies to better understand the mechanisms of the antioxidant properties of Cs.

Conclusion: Altogether, the results indicate that Cs can be used as important sources of antioxidants that have diverse potentials in therapeutic uses, which should be further investigated in the area of health and medicine.

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Introduction

Oxidative stress (OS) is defined as unbalanced generation of reactive oxygen species (ROS) and the capabilities of the body to detoxify the reactive intermediates or handle the damage it generates. Such imbalance causes oxidative damage to other biomolecules, including lipids, proteins, and DNA, thus impairing the structure and functioning of the cells (García-Sánchez et al. 2020). Mounting evidence indicates that OS is at the center of the pathophysiology of a broad range of chronic diseases, such as cardiovascular diseases, diabetes mellitus, neurodegenerative conditions (e.g. Alzheimer and Parkinson diseases), and a variety of cancers. Long-term oxidative stress leads to chronic inflammation, mitochondrial dysfunction, and gene expression changes, which causes the onset and progression of the disease (García-Sánchez et al. 2020).

Pharmacological interventions of chronic diseases can affect the level of oxidative stress either increasing or preventing oxidative stress. As an illustration, antihypertensive and lipid-lowering treatments have the potential of alleviate oxidative stress, which offers an added cardiovascular cover. On the other hand, specific immunosuppressive therapies of cancer or infectious diseases have the effect of enhancing production of ROS, which lead to significant oxidative effects (Pizzino et al. 2017). The ability to control and treat OS using antioxidant therapies or lifestyle changes is thus an important approach in preventive and curative strategies of the disease (García-Sánchez et al. 2020; Reddy 2023).

In recent years, natural products received much interest as rich sources of bioactive compounds of potent antioxidant activity. *Crocus sativus* (Cs), or saffron, is particularly interesting because of its complex phytochemical composition (Moratalla-López et al. 2019). Cs exhibits significant antioxidant activity primarily due to its bioactive constituents such as crocin, crocetin, and safranal. These compounds effectively scavenge free radicals and reduce oxidative stress, thereby protecting cells from damage. The antioxidant properties of saffron contribute to its neuroprotective, anti-inflammatory, and hepatoprotective effects (Abedi et al. 2023; Kumar, Sharma and Jain 2024; Moratalla-López et al. 2019).

This comprehensive review systematically evaluates the phytochemical constituents of Cs with a focus on their antioxidant activities, based on both experimental and clinical studies. By integrating recent findings on the bioactivity and bioavailability of Cs metabolites, this review aims to illuminate the molecular mechanisms underlying Cs protective effects against oxidative damage and to highlight its potential application in managing oxidative stress-mediated disorders.

Phytochemicals analysis of *Crocus sativus*

The phytochemistry of Cs is dominated by three principal active compounds: crocin, picrocrocin, and safranal. These bioactive apocarotenoids define the quality and therapeutic potential of saffron and have been subject to extensive analytical and pharmacological characterization. However, the plant contains several other constituents too.

Crocin

Crocin is the main active compound found in Cs which gives the spice bright golden-yellow color. This compound belongs to a group of natural chemicals called carotenoid glycosides and is responsible for many of Cs health benefits. Distinct from the majority of carotenoids, which exhibit lipophilicity, crocin is uniquely hydrophilic due to the presence of glycosidic sugar moieties in its molecular structure (Tung et al. 2022).

There are several types of crocin, named crocin-1 through crocin-4, which differ in how many glucose sugar units they have and where these sugars attach to the crocetin molecule. Crocin's chemical formula is $C_{44}H_{64}O_{24}$, with a molecular weight near 977 grams per mole (Mykhailenko et al. 2019). It is biosynthesized in the plant through a process that starts with the splitting of a carotenoid called zeaxanthin by specific enzymes, followed by the addition of sugar molecules that make crocin water-soluble and biologically active. This pathway is related to the creation of other saffron compounds like picrocrocin and safranal (Mykhailenko et al. 2019; Tung et al. 2022).

Crocin absorbs light most strongly at 440 nm wavelength, which is used to measure Cs quality. Because it dissolves in water, crocin is better absorbed and spread in the body than typical fat-soluble carotenoids (Aissa et al. 2023; Christodoulou et al. 2015). This property makes it especially useful in medical and health applications.

One of crocin's key benefits is its powerful antioxidant effect. It neutralizes harmful ROS, prevents damage to fats in cells, and boosts the body's own antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Crocin can protect brain, liver, kidney, and heart tissues from oxidative stress. It protect nerve cells after injuries caused by disorders involving impaired blood flow, and may also have potential in treating diseases like Alzheimer's and Parkinson's (Aissa et al. 2023; Anaeigoudari, Anaeigoudari and Kheirkhah-Vakilabad 2023). Although crocin's water solubility improves its absorption, some of it is broken down into crocetin in the digestive system, which can limit how much crocin enters the bloodstream. Still, both crocin and its breakdown products are known to offer protective health effects. Crocin is fairly stable when exposed to heat and acidic conditions but can degrade if kept in alkaline environments or under prolonged light, so careful storage is important for its use in therapies (Aissa et al. 2023).

Today, crocin is being explored for treating various health issues, including nerve diseases, heart problems, cancer, and metabolic disorders. Its antioxidant and anti-inflammatory properties contribute to these benefits. Because it comes from a natural source and has a good safety record, crocin is a promising therapeutic agent for herbal medicine and drug development.

Picrocrocin

Picrocrocin is a key natural product in Cs, it makes this spice have a bitter flavor. Content of picrocrocin constitutes in the plant is approximately 1 to 5 percent of the dry mass of saffron which again depends on the type of harvest and processing of the saffron. It does not have a color and can be dissolved easily in water because of sugar content, which makes it different among most plant chemicals (Butnariu et al. 2022). Picrocrocin is converted to safranal by enzyme action when the saffron is dried and stored, thus giving the characteristic aroma of saffron. Measurement of picrocrocin is a common procedure is significant in the determination of the quality of saffron (Avila-Sosa et al. 2022). Other than base flavoring and aroma to saffron, picrocrocin is a potent antioxidant. It aids in neutralizing the toxic effects of ROS and shields against cellular oxidative damage by propping-up endogenous antioxidant enzymes, like SOD, CAT and GPx (Cerdá-Bernad et al. 2022). This antioxidant property has led to traditional medicinal application of saffron and also has attracted contemporary scientific attention because it theoretically has a protective effect in the brain and heart (Beigoli et al. 2024). Picrocrocin can potentially protect nerve cells by alleviating anxiety and seizures potentially due to its capacity to prevalent the brain and other organs oxidative stress. These effects indicate that it may help to treat conditions in the nerve system such as epilepsy, depression and neurodegenerative disorders. Also, animal studies have found that picrocrocin could help keep the heart healthy by shielding the heart tissue against oxidative damage and enhancing the levels of blood fat.

Safranal

Synthetically, safranal is a compound of monoterpene aldehyde of formula $C_{10}H_{14}O$ whose its structure is described as 2,6,6-trimethyl-1,3-cyclohexadiene-1-carboxaldehyde (Avila-Sosa et al. 2022). Safranal forms approximately 0.4 to 0.5 percent of the dry weight of saffron and is up to 30 percent to 70 percent of the essential oils obtained out of saffron, depending on the processing and storage of the spice (Rezaee and Hosseinzadeh 2013). As a volatile compound, the sweet smell of hay is a central value attribute of safranal in culinary use as a cooking and perfume ingredient, as well as an in medicinal uses. It is characteristically absorptive of ultra-violet in the region of 330 nm, the feature taken advantage of in laboratories in determining the purity and quality of saffron. Besides its smell, interest in safranal has been high owing to its strong biological properties (Rezaee and Hosseinzadeh 2013). It may act as an antioxidant as it prevents the damage of the cells within a body by neutralizing dangerous ROS and by influencing the pathways associated with oxidative stress. This is attributable to the antioxidant activity that aids in giving it the protection potential seen in its laboratory and animal studies against ailments such as neurodegenerative diseases, and heart diseases that have been associated with oxidative stress (Cerdá-Bernad et al. 2022). Moreover, safranal has also been demonstrated to possess anti-inflammatory and neuroprotective effects, indicating its value in the context of further health-related studies and applications.

Carotenoids

Carotenoids are a large family of natural pigments made by plants, algae, fungi, and some bacteria. These pigments are responsible for the bright yellow, orange, and red colors seen in many fruits, vegetables, and flowers. Chemically, carotenoids are made up of eight linked isoprene units, forming molecules with 40 carbon atoms. They have a long chain of double bonds that gives them their vibrant color and also makes them chemically reactive and sensitive to light, oxygen, and acidic environments (Sun et al. 2022).

In plants, carotenoids are produced through a multi-step process starting with the joining of two molecules called geranylgeranyl pyrophosphate (GGPP) to form phytoene. This step is controlled by the enzyme phytoene synthase and is important for regulating how much carotenoid is made. Phytoene is then transformed through several changes into lycopene, a bright red pigment. Lycopene is further modified to create other carotenoids like α-carotene and β-carotene, and then these can be changed into xanthophylls such as lutein, zeaxanthin, and violaxanthin (Sun et al. 2022).

Besides providing color, carotenoids are also the starting point for the production of important signaling molecules in plants, like the hormone abscisic acid (ABA) and strigolactones, which help regulate growth and how plants respond to stress. Special enzymes known as carotenoid cleavage dioxygenases cut carotenoids into smaller pieces that play diverse roles in plant development and defense (Sun et al. 2022). Due to the significance of their functions, the concentrations of carotenoids in plants are strictly regulated at many points, such as the expression of genes that induce the synthesis of carotenoids, as well as the storage of these compounds by the cells of the plant. Scientists are also seeking methods to raise carotenoid material in plants so as to bring up their nutritional value and optimize its tolerance to ecological stress (Sun et al. 2022).

Essentially, carotenoids are multifunctional natural compounds vital in plants and human beings. They play a role in pigmentation in plants, regulation of growth and shielding against stress as well as a good health value in people as antioxidants and sources of vitamin A. Further research is still being done to establish the complete therapeutic value of the various characteristics of the mixtures and how the benefits of these mixtures can be realized in diet and farming practices.

Flavonoids

Cs has been reported as containing important disease-preventive compounds such as flavonoids which have multiple health benefits. Important flavonoids presented in saffron extracts are quercetin, kaempferol, luteolin, rutin, and hesperidin. It is a widely known fact about such compounds that they have good antioxidant, anti-inflammatory, and blood vessel protective characteristics that significantly add to the healing power of saffron (Qadir et al. 2024).

Chemically, flavonoids can be considered as part of a huge family of polyphenols containing a compound structure characterized by two aromatic rings (designated A and B) linked by the third one (containing oxygen) (C ring). A variety of flavonoids varies about the design of the hydroxyls groups and sugar attachments, which result in flavones, flavonols, and flavanones. A lot of these can be found in the petals and stigmas of saffron. Kaempferol and quercetin are predominant flavonols that have the reputation to effectively counteract the negative impacts of harmful free radicals and also to control the internal antioxidant defense mechanisms of the body (Qadir et al. 2024).

Laboratory and animal-based scientific research has demonstrated that flavonoids found in saffron are powerful in neutralizing ROS, a key cause of cell damage and inflammation (Ye et al. 2021). These flavonoids increase key antioxidant enzymes such as SOD, CAT and GPx and aid in cell protection.

A single flavonoid isolated in saffron petals, kaempferol-3-O-sophoroside, is also associated to safeguarding the liver via the regulation of genes leading to antioxidant activity, cell survival, and inflammation. Likewise, rutin or hesperidin, which are also flavonoid sugar compounds, promotes cardiovascular health by strengthening the walls of blood vessels, thereby decreasing issues with the inner lining of the blood vessels as well as lowering inflammation, which can prevent heart diseases (Ye et al. 2021).

Besides being antioxidants and inflammation-reducing substances Cs flavonoids have also been identified to protect nerve cells. They are capable to enter the brain and affecting pathways affecting the survival of the neurons, and thus, curing or averting neurodegenerative disorders such as Alzheimer and Parkinson (Hatziagapiou et al. 2019). All this variety of flavonoids can bring another valuable addition to the complex combination of useful substances in saffron, including phytochemicals such as carotenoids like crocin. These molecules in combination form a potent blend that explains the reason why saffron has a wide range of health benefits as well as why it is traditionally and increasingly becoming a part of natural medicine.

Tannins

Cs also contains tannins (natural polyphenolic compound s) in different levels. They are central to the health value of saffron, and in particular its ability to exert anti-inflammatory and antimicrobial activities. Tannins have the reputation of binding and precipitating proteins which forms the principle behind much of their biological functions (Kumar, Sharma and Jain 2024). Tannins are known to be of two large groups chemically: hydrolyzable tannins which consist of either gallic acid or ellagic acid bonded to a sugar molecule; and condensed tannins (sometimes referred to as proanthocyanidins) which consist of chains of flavan-3-ol types (Kumar et al. 2024). Most tannins in saffron are of the hydrolyzable type and form part of the numerous phenolic compounds making saffron exhibits the remedial features. Experiments focusing on the extraction process indicate that the quantity of tannins in saffron are different from each other based on the solvent employed. Take an example, ethyl acetate or water extract has been found to be exposed to more tannins than that of standard gallic acid levels, which implies that tannins are extracted very well under polar solvents (Bellachioma et al. 2022). Type and volume of tannins and of other phenols extracted from saffron are highly influenced by the use of extraction method. The major anti-inflammatory properties of tannins are attributable to feedback on enzymes and mediators of inflammation abatement, including cyclooxygenase (COX) and lipoxygenase (LOX) (Hossain et al. 2021). They contribute to a reduction in body pro-inflammatory chemicals thereby minimizing the general response to inflammation. In a number of laboratory and animal studies, saffron tannins have proven to be effective in reducing inflammation hence offering support to its traditional use in inflammatory conditions. Also tannins showed great antimicrobial anti-fungi, and anti-viruses powers agents. They accomplish it when they attach to proteins on microbial surface, break their cell membranes, and prevent the necessary enzymes, which compromises microbial growth and infection. Saffron through its tannins compounds, have the ability to prevent many prevalent infections, and therefore, it is used in treating infections (Fraga-Corral et al. 2021; Hossain et al. 2021).

Also, the tannins complement the action of other phenolic compounds such as flavonoids and phenolic acids in saffron to enhance the antioxidant potential of saffron. This affects inflammation and microbial harm reduction because they can neutralize pernicious ROS and forestall oxidative harm to tissues (Hossain et al. 2021). Generally, tannins are significant number of phytochemical in saffron which makes significant contributions to health benefits of the plant, particularly its anti-inflammatory and antimicrobial effects.

Phenolic compounds and glycosides

One of the major natural chemicals, of Cs is the phenolic compounds and glycosides, which are significant contributors to health benefits. It is well established that phenolic compounds possess strong antioxidant and anti-inflammatory properties that shield the cells against oxidative damage of harmful molecules and alleviate inflammation. Research has established that saffron contains phenols which have the ability to reduce inflammatory compounds such as cytokines and nitric oxide favoring its ancient applications in the treatment of inflammatory cases (Frusciante et al. 2024).

Glycosides particularly cardiac glycosides play a significant role on the health of the heart because they enhance the strength of the heart muscles to contract and the provision of rhythmic contractions by the heart muscles. These are natural products which are cardiac tonics with potential to maintain cardiovascular function (Esmaeili et al. 2011).

The combination of these substances further increases the total medicinal value of saffron since they exert antioxidant, anti-inflammatory, and cardiovascular protective properties. These compounds are located in varying section of the saffron plant such as the stigmas and the flowers.

Other constituents

Cs is not only abundant in famous carotenoids also it contain valuable nutrients such as amino acids, sugars, proteins, minerals, and vitamins such as thiamine (vitamin B1), and riboflavin (vitamin B2) (Kumar, Sharma and Jain 2024). These are some of the substances that contribute to the nutritional value and general health effects of saffron (Kianmehr et al. 2022). Such nutrients, besides the glycosides harboring, contain potent bioactive compounds such as crocin and safranal, make saffron a functional food with therapeutic potential. Also, the essential minerals such as potassium and magnesium in saffron further favor its capacity as a source of good health and wellness.

Overall, studies have proved the high antioxidant characteristics of Cs and its phytochemicals which is vital in the opposition of oxidative stress among which being a primary precursor of several chronic diseases. Cs strong antioxidant properties prevent cell damage by reactive free radicals, thus decreasing inflammation and promoting general cellular health. The protective roles indicate a possible application of the Cs extracts in the treatment and prevention of several illnesses such as neurodegenerative diseases, cardiovascular diseases, and cancer in some cases. Figure 1 and Table 1 presenting major phytochemicals of *Crocus sativus*.

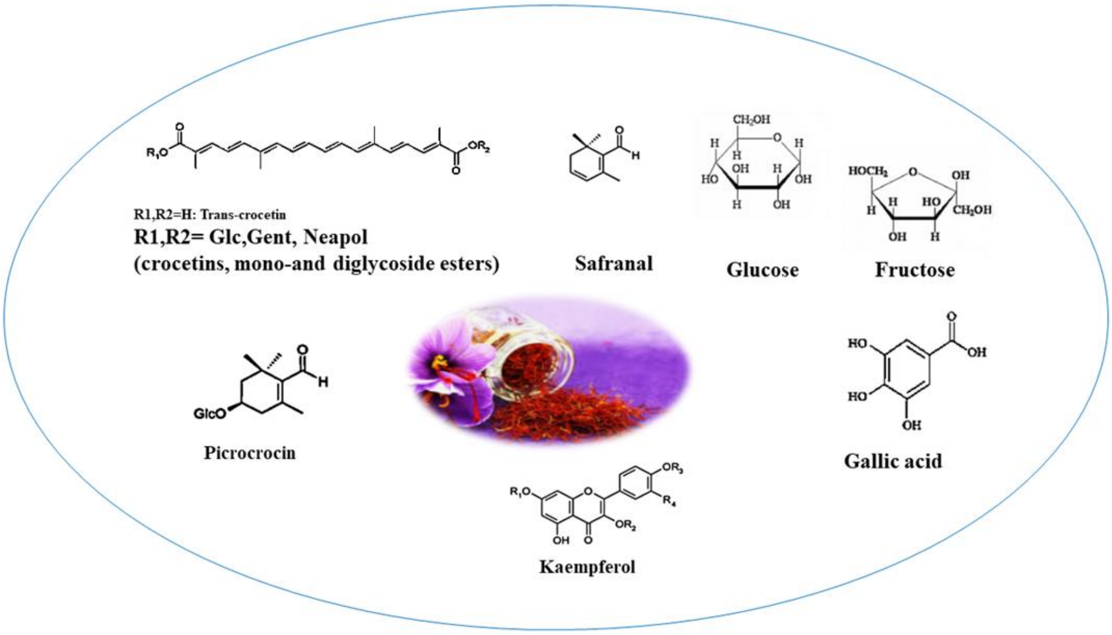

Figure 1. Overview of the phytochemicals from *Crocus sativus*

Table 1. Summary of the major phytochemicals of *Crocus sativus*

Phytochemical	Approximate Content (%)	Key Properties	Chemical Structure	Ref
Crocin	6–16% (dry stigma weight)	Carotenoid pigment responsible for saffron's color, antioxidant	Glycosylated crocetin (diester of crocetin and sugars)	(Aissa et al. 2023; Gonda et al. 2012; Song et al. 2021)
Picrocrocin	Spanish: 0.79–12.94% (dry weight) Iranian: 2.18–6.15% (dry weight) Indian: 1.07–2.16% (dry weight)	Monoterpene glycoside, bitter taste precursor to safranal	$C_{16}H_{26}O_7$ Glucoside of safranal (monoterpene aldehyde)	(Kumar et al. 2024; Nazarian et al. 2021)
Safranal	0.1–0.5%	Volatile compound giving saffron aroma, antioxidant	$C_{10}H_{14}O$ Monoterpene aldehyde	(Aissa et al. 2023; Avila-Sosa et al. 2022)
Flavonoids	0.2–0.5%	Antioxidant, anti-inflammatory	Flavones and flavonols such as kaempferol, quercetin derivatives	(Kumar et al. 2024)
Phenolic compounds	0.1–0.6%	Antioxidant, antimicrobial	Phenolic acids like gallic acid, caffeic acid	(Aissa et al. 2023; Karimi et al. 2010)
Tannins	Trace to 0.5%	Astringent, anti-inflammatory, antimicrobial	Polyphenolic polymers (hydrolyzable/condensed types)	(Hosseini et al. 2018; Kumar et al. 2024; Maqbool et al. 2022)
Sugars	~63%	Nutritional energy source	Glucose, fructose	(Aissa et al. 2023; Cerdá-Bernad et al. 2023; Hosseini, Razavi and Hosseinzadeh 2018)
Proteins and amino acids	12–14%	Structural, enzymatic functions	Various amino acids including aspartic acid, leucine	(Aissa et al. 2023; Paredi et al. 2016)
Minerals	~5%	Essential for cellular functions	Potassium, magnesium, calcium, iron	(Aissa et al. 2023)
Vitamins	Trace amounts	Nutritional and enzymatic cofactors	Thiamine (B1), riboflavin (B2)	(Avila-Sosa et al. 2022)

Materials and Methods

Search strategy and inclusion criteria

The databases relied upon in this study included Scopus, WOS, and PubMed. Figure 2 displays the collection of all publications, including *in vitro*, *in vivo*, and clinical trials, until the end of October 2025. The following terms were used in the search: "*Crocus sativus* "cardiovascular disorders", "cancer and neoplasia", "endocrine and metabolic disorders", "gastrointestinal disorders", "liver disorders", "immunological disorders", "autoimmune disorders", "neurologic disorders", "respiratory disorders", "urogenital disorders", "antioxidant activities". The following items were considered as criteria for inclusion; 1) Articles that examined the experimental and clinical evidences on the antioxidant activities of *C. sativus*. 2) Research utilizing *in vitro* models, animal models, or human volunteers. 3) Articles published in the academic journals that have passed the rigorous peer-review process. The eliminated items from consideration were; 1) Publications in languages that were not English. 2) Research that failed to focus on the impacts of Cs on oxidative stress. 3) Articles that were not peer-reviewed, including conference abstracts, editorials, and letters.

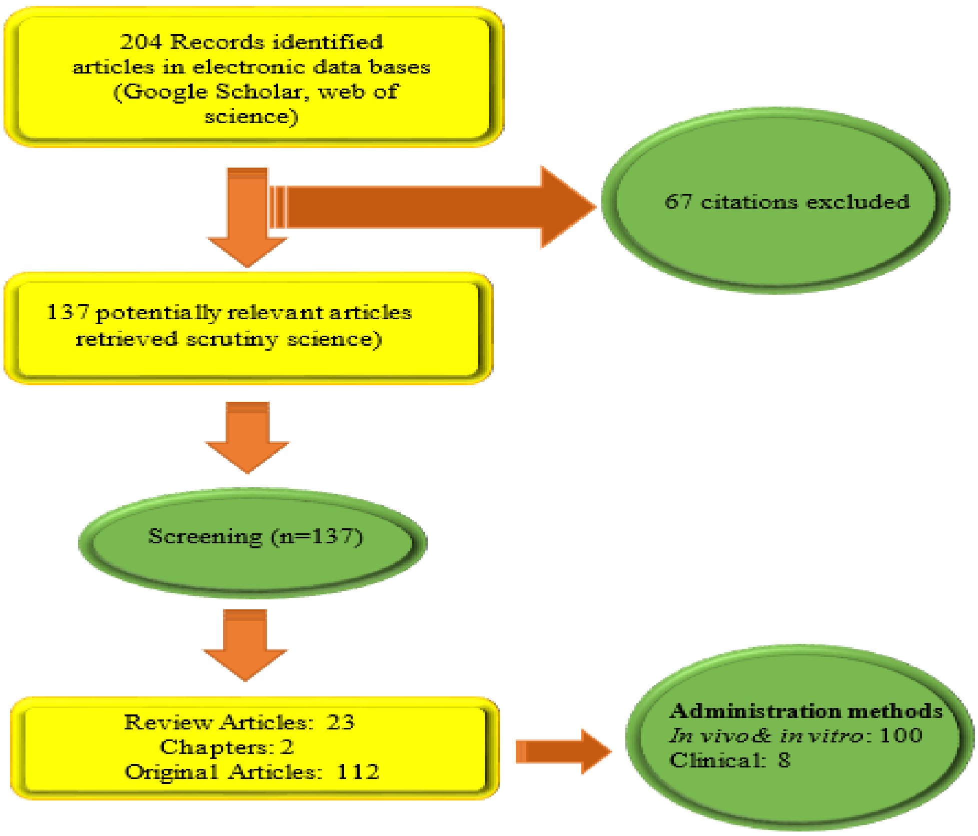

Figure 2. Selection of the studies flowchart of the process for the review

Results

Antioxidant effect of *Crocus sativus* extracts and essential oil

Researches have indicated that various extracts of Cs possess notable antioxidant activities (Boskabady and Farkhondeh 2016). Assimopoulou et al. examined the radical scavenging activity of Cs grown in Kozani, Greece using a diphenylpicrylhydrazyl (DPPH) assay. At a level of 2000 ppm, saffron methanolic extract (SME) displayed notable antioxidant characteristics (Assimopoulou et al. 2005). The antioxidant activity of Cs stigma aqueous and ethanolic extract through deoxyribose assay and erythrocyte membrane lipid peroxidation *in vitro*, showed its antioxidant potential of various concentrations ranging from 10 to 1000 µg/ml (Hosseinzadeh, Shamsaie and Mehri 2009). The Cs essential oils, antimicrobial and antioxidant characteristics make it a valuable resource for the food industry antioxidant characteristics (Ahmed et al. 2016).

In vitro studies

Cardiovascular disorders

Cs is a source of valuable antioxidants (crocin and crocetin) crucial to the prevention and therapy of cardiovascular diseases. Many compounds of plant have been reported to have antioxidant effects and combat various diseases related to oxidative stress such as cardiovascular disease. Furthermore; research has indicated that in addition to the benefits Cs listed above there may be additional cardio-protective effects, mainly, improving lipid profiles, decrease blood pressure and improved endothelial functioning (Yan et al. 2024).

The antioxidant characteristics of Cs aqueous extract (500 µg/ml) were demonstrated in HUVEC cells through the DPPH assay, indicating protection against oxidative stress. Cs has been shown to act as both an immediate antioxidant and a modulator of micro-RNAs and RNA expression in response to stressful conditions. These effects collectively improve cell survival and highlight the potential role of Cs in preventing and treating diseases associated with oxidative stress (Rodriguez-Ruiz et al. 2016).

A study investigated the Cs aqueous extract's antioxidant characteristics on H9c2 cardiomyocytes against ischemia-reperfusion (I/R) and doxorubicin (DOX) toxicity. DOX, known for its anticancer properties, poses cardiac risks through oxidative stress, especially in those with ischemic heart disease. The study found that DOX-induced cardiac toxicity under I/R conditions decreased cell viability, blocked cardio-protective pathways, decreased contractile proteins, increased apoptotic markers, and induced mitochondrial dysfunction. Cs extract at a 10 µg/ml concentration prevented cardiac damage, maintained cell viability, and reduced oxidative stress (Chahine et al. 2016). Cs exhibits potent antioxidant characteristics, with 68% inhibition at 500 µg/ml concentration, suggesting potential benefits for cardiovascular health *in vitro* (Mohd Hatta et al. 2023). Antioxidants have the potential to prevent cardiovascular disease by blocking apoptotic signaling pathways and decreasing cell death in the heart muscle. Cs can prevent the decrease in B-cell lymphoma protein 2 (Bcl-2) gene expression and decrease apoptosis in a manner dose-dependently (Mehri et al. 2012). Cs extracts have been shown to protect against cardio-toxicity during ischemic conditions through antioxidant and anti-apoptotic mechanisms. It acts as an efficient antiplatelet phytochemical, preventing oxidative stress-induced apoptosis and inhibiting platelet aggregation, ultimately playing a crucial role in cardiovascular protection (Nanda and Madan 2021).

The importance of these effects cannot be overstated in halting the advancement of cardiovascular diseases and enhancing overall heart wellness. Although further research is required to comprehensively grasp the mechanisms behind these advantages, the antioxidant qualities of Cs offer hope in potentially lessening the likelihood of cardiovascular disorders. While the antioxidant benefits of Cs are widely acknowledged, certain studies propose that the effectiveness of these extracts may differ depending on dosage and individual health circumstances, highlighting the necessity for additional research to refine therapeutic uses. A brief description of the antioxidant characteristics of C*s* extracts on cardiovascular disorders was provided in Table 2.

Table 2. Antioxidant effects of *Crocus sativus* extracts and essential oil on *in vitro* studies

Type of study	Disorders	Experimental model	Dose, Duration	Effect	Ref.
In vitro studies	Cardio Vascular	HUVECs line	500 µg/ml	↑ Antioxidant characteristics	(Rodriguez-Ruiz et al. 2016)
		H9c2 cell line	10 µg/ml	↓Oxidative stress ↑Cell viability	(Chahine et al. 2016)
		MDA-MB-468 cell line AGS cell line U87 cell line MCF10-A cell line	0.5, 1, 1.5, 3 mg/ml	↑Expression of Bax ↓Expression of Bcl2 genes	(Behdani and Hoshyar 2016)
		HT-29 cell line	50-250 µg/ml	↓Oxidative stress and inflammation	(Nourbakhsh et al. 2020)
		HT-22 cell line L929 cell line	65-90 mg/g	No antioxidant capacity	(Soylu 2024)
	Endocrine and metabolic	PC12 cells	5, 25 mg/ml	Antioxidant ↓Glucose toxicity	(Mousavi et al. 2010)
		-	400 ppm	Antioxidant Hypolipidemic	(Rahardhian et al. 2020)
		RIN-5F cell line L6 cell line	200, 400 µg/ml	↑Radical scavenging activity ↑Insulin secretion ↑Glucose uptake ↑GLUT4 and AMPKα expression	(Dehghan et al. 2016)
	Gastro intestinal and liver	BRL-3A cell line	100 µg/ml of TFESP	↓ROS levels Modulate SOD, CAT, GSH ↑Expression of antioxidant genes	(Ye et al. 2021)
	General health	Tissues from kidney, liver, lungs and heart	0.45 mg/ml	Antioxidant ↓LP level ↑SOD activity	(Makhlouf et al. 2011)
	Neurologic	Stigmas of *Cs*	300, 600 µg/ml 20 minutes	↓Aβ fibrillogenesis Antioxidant	(Papandreou et al. 2006)
	Urogenital	IVM and IVF	5, 10, 40 mg/ml	Antioxidant ↑IVM rates ↑IVF rates	(Maleki et al. 2014)

Abbreviations: Ref: references, HUVECs: human umbilical vein endothelial cells, RNA: ribonucleic acid, H9c2: rat embryonic ventricular cardiomyocyte cell line, PNT1A: normal prostate cell line, 22Rv1: early stages of prostate cancer cell line, PC-3: late stages of prostate cancer cell line, MDA-MB-468: breast cancer cell line, AGS: stomach cancer cell line, U87: brain cancer cell line, MCF10-A: normal epithelial cell line, Bax: Bcl-2-associated X protein, Bcl-2: B-cell lymphoma protein 2, HT-29: colorectal cancer cell line, HT-22: malignant colon cancer cell line, L929: non-malignant fibroblast cell line, PC12: pheochromocytoma cells, RIN-5F: rat pancreatic beta cell line, L6: rat L6 myoblast cell line, GLUT4: glucose transporter type 4, AMPKα: adenosine monophosphate-activated protein kinase α, TFESP: total flavonoid extracts from saffron petals, BRL-3A: rat liver cell line, ROS: reactive oxygen species, SOD: superoxide dismutase, CAT: catalase, GSH: glutathione, LP: lipid peroxidation, Cs: *Crocus sativus*, Aβ: amyloid beta-peptide, SH-SY5Y: human neuroblastoma cell line, H2O2: hydrogen peroxide, IVM: *in vitro* maturation, IVF: *in vitro* fertilization.

Cancer and neoplasia

The impact of four different Cs aqueous extracts (65-90 mg/g) on malignant HT-22 and non-malignant L929 cell lines was studied by measuring DPPH, ferric ion reducing antioxidant power (FRAP), total polyphenol, and flavonoid levels to assess their antioxidant and cytotoxic effects. The results did not show antioxidant capacity while demonstrated significant anti-proliferation effect of Cs leading to cytotoxic activity against HT-22 cell lines (Soylu 2024).

Cs stigma (0.5, 1, 1.5 and 3 mg/ml) effects on cancer cells were reviewed by its anti-oxidant property. Organic Cs ethanolic extract showed higher secondary metabolites, antioxidants, and cytotoxicity in comparison to the inorganic Cs. TCs, through its organic Cs, was able to suppress the viability of cancer cells on a dose and time dependent basis. Inducing cancer cell apoptosis of the plant was shown by activating the Bcl-2-associated X protein (Bax) with the down-regulation of Bcl2 genes. These results suggest that organic Cs has cancer cell proliferation inhibitory potential in a selective manner (Behdani and Hoshyar 2016).

Colorectal cancer (HT-29) and normal human fibroblasts were cultured in RPMI 1640 and exposed to 8 Gy dose of X-rays after treatment with various doses of Cs methanol extracts (50 to 250 µg/ml). Cs treatment, inhibited the growth of HT-29 cell line and effectively ameliorated oxidative stress and inflammation. Besides, Cs antioxidants increased the effectiveness of radiation therapy and became radiation-sensitizing agents by increasing the sensitivity of cancer cells to death caused by radiation (Nourbakhsh et al. 2020).

On the overall scale, studies unravel that Cs bear antioxidant properties that can fight cancer related free radicals. In addition, Cs has been proved to hinder the proliferation and expansion of cancerous cells and induce programmed cell death or apoptosis in such cellular formations. The outcomes show that Cs has an opportunity to provide protection and therapeutic support in combating cancer and neoplasia. Table 2 gives a brief description on the antioxidant properties of Cs extracts against cancer and neoplasia.

Endocrine and metabolic disorders

Oxidative stress has a strong influence in the development of insulin resistance diabetes mellitus (DM) (Yaribeygi et al. 2020). Cs aqueous extract effect on a cellular model (PC12 cells) that represents a diabetic neuropathy study. The cells were incubated with different glucose concentrations (13.5 mg/ml and 27 mg/ml) that reduced cell viability as a result of increasing ROS production. Pre-treatment of PC12 cells with Cs extract (5 and 25 mg/ml) prior to treatment with high glucose concentration showed that the extract works as a protective agent against its toxicity (Mousavi et al. 2010).

Cs ethanolic extract was examined for its antioxidant and anti-cholesterol capabilities in a study. Various concentrations were tested, revealing that a concentration of 400 ppm was the most effective in reducing cholesterol levels. Cs demonstrates significant antioxidant and hypo-lipidemic properties by reducing lipid profile factors while enhancing the activity of antioxidant enzymes (Rahardhian et al. 2020).

FRAP and DPPH radical scavenging assays were used to determine antioxidant capacity with varying doses (200 and 400 0g/ml) of hydroalcoholic Cs extract ovincubated in rat pancreatic beta cell line (RIN-5F) and rat L6 myoblast cell line (L6). Cs extract significantly increased radical scavenging activity, insulin secretion, glucose uptake, and up-regulation in glucose transporter type 4 (GLUT4) and adenosine monophosphate-activated protein kinase α (AMPK 1). These findings further highlight the outstanding antioxidative and antidiabetic value of Cs (Dehghan et al. 2016).

In vitro studies have demonstrated that Cs extracts can modulate endocrine and metabolic disturbances, indicating that antioxidant effects that may help protect against oxidative stress-related diseases. These results indicate that Cs may be beneficial in managing conditions such as diabetes and cardiovascular diseases by regulating hormone levels and improving antioxidant defense mechanisms. A brief description of the antioxidant characteristics of Cs extracts on endocrine and metabolic disorders is provided in Table 2.

Gastrointestinal and liver disorders

Extensive evidence demonstrates that oxidative stress plays an important role in the etiology of various liver diseases and antioxidant treatments has been proven to be effective in the treatment of these diseases (Li et al. 2015). Studies suggest that Cs may act as a protective antioxidant against multiple liver diseases (Sumaiya et al. 2020).

A normal rat liver cell line (BRL-3A) was used as an oxidative damage model (with tert-butyl peroxide, t-BHP) for assessing the hepato-protective properties of Cs. DPPH and 2, 2-azino-bis- 3-ethyl benzothiazoline-6-sulphonic acid (ABTS) radical scavenging technique was used to determine the levels of antioxidants, and the intra-cellular levels of ROS were determined with 2, 7-dichlorodihydrofluorescein diacetate (DCFH-DA). The outcomes indicated increasing antioxidant potential of total flavonoid extracts of petals (TFESP), stamens (TFESS) and a mixture of both (TFEMS). Interestingly, the intervention of 100 µg/ml of TFESP showed a hepato-protective effect, decreasing the level of ROS and regulating cognate enzymes putatively, including SOD, CAT, and glutathione (GSH), in addition to up-regulating antioxidant gene expressions (Ye et al. 2021). A brief description of the antioxidant characteristics of Cs extracts on gastrointestinal and liver disorders is provided in Table 2.

General health

A study assessed different ethanolic extracts of Lebanese Cs to determine their *in vitro* antioxidant effects. Tissues from various organs including kidney, liver, lungs, and heart were analyzed for the antioxidant effects of Cs using lipid peroxidation (LP) and SOD activity. Results indicated that Cs extract exhibits a dose-dependent antioxidant effect, with optimal efficacy observed at a concentration of 0.45 mg/ml (Makhlouf et al. 2011). A brief description of the antioxidant characteristics of Cs extracts on general health is provided in Table 2.

Neurologic disorders

Neurodegenerative diseases are significantly impacted by oxidative stress, highlighting the importance of antioxidants in their control (Teleanu et al. 2022). Oxidative stress is central to the pathogenesis of Alzheimer disease (AD) that is manifested by the accumulation of amyloid beta (Aβ) and Tau protein in the CNS (Tamagno et al. 2021).

Studies have suggested that Cs may be able to improve cognitive function, memory, and mood in individuals with autoimmune diseases. Additionally, Cs has demonstrated its ability to protect neurons, helping to prevent further damage to brain cells and potentially slowing the progression of neurologic disorders. While the research on Cs's antioxidant effects on neurologic disorders is still relatively new, the potential benefits of this spice in improving brain health are promising. As we continue to better understand the mechanisms behind these effects, Cs could emerge as a natural and effective adjunct treatment for individuals with neurologic disorders. Additional studies are necessary to determine the most effective amount and composition of Cs for therapeutic applications, although early indications show that including this spice in diet may benefit brain function and overall neurological health. These studies collectively underscore the potential of Cs and its constituents as therapeutic agents in combating oxidative stress-related neurodegenerative diseases. A brief description of the antioxidant characteristics of Cs extracts on neurologic disorders is provided in Table 2.

Urogenital disorders

As it was indicated in the review by Maleki et al., different dosages of Saffron aqueous extract (SAE) (5 mg/ml, 10 mg/ml, and 40 mg/ml) were evaluated for their impacts on *in vitro* maturation (IVM) and *in* *vitro* fertilization (IVF). It is proved to be the most effective at a concentration of 40 mg/ml, enhancing the rates of IVM and IVF compared to the control group (Maleki et al. 2014). Cs could be considered as a potent agent to contribute urogenital health by maximizing the reduction of oxidative stress and inflammation of the urinary and reproductive systems, however the inquiry should be extended to understand fully the inner workings of the antioxidant nature of Cs and the potential clinical applications of Cs in urogenital treatment. A brief description of the antioxidant characteristics of Cs extracts on urogenital disorders is provided in Table 2.

In vivo studies

Cardiovascular disorders

The effects of Cs aqueous extract administered at varying doses (2.5, 5, and 10 mg/kg, intravenously) on blood pressure regulation in normotensive and hypertensive rat models were examined. The study revealed a considerable reduction in mean arterial pressure (MABP), especially at the highest dosage of 10 mg/kg. Although the study suggests a correlation between the extract's antioxidant characteristics and the observed antihypertensive effects, specific antioxidant parameters were not identified (Imenshahidi et al. 2010).

Cs aqueous extract (100 mg/kg, 7 days, orally) was used to examine the effects in injured male Wistar rat hearts subjected to isoproterenol (ISO)-induced myocardial injury. The rats were categorized into four sets: control, ISO, Cs and Cs + ISO. ISO raised the troponin I and lowered the GPx in the heart. The Cs + ISO group had lower levels of tissue destruction and troponin I than in the ISO group. These findings implied that Cs could protect cardiac tissue against oxidation damage as a result of its antioxidant properties (Joukar et al. 2010). The cardio-protective and antioxidant effect of Cs aqueous extract against ISO-induced myocardial damage in male Wistar rats was investigated by assigning them to five common groups, namely, a control, ISO, and three Cs-extract groups which were administered 200, 400, and 800 mg/kg of Cs extract orally daily, over 30 days. Cs effectively reduced oxidative stress markers but increased the activity of antioxidant enzymes especially at a dose of 400 mg/kg, demonstrating its importance in maintaining the redox balance of the cells and protection of the heart to oxidant harm (Sachdeva et al. 2012a). Cs aqueous extracts protection effects on isolated rabbit hearts subjected to acute heart toxicity induced by DOX were examined. Higher dose (10 µg/ml, perfused during 5 min through the coronary circulation via the aortic cannula) of Cs extracts administered during reperfusion phase after the acute toxicity significantly mitigated oxidative injury, mort ha its administration prior to ischemia. This was associated with suppression of the p38 mitogen-activated protein kinase (p38 MAPK) signaling pathway and activation of the Ak strain transforming/mammalian target of rapamycin/4E-binding protein 1(AKT/mTOR/4EBP1) signaling pathway, eventually maintaining the integrity of cardiac troponin T protein. In general, Cs alleviated DOX induced oxidative stress and cardio-protection by its antioxidant and anti-apoptotic effects (Chahine et al. 2014).

The results of Cs on rabbit myocardial injury due to I/R, showed that giving Cs aqueous extract orally improved left ventricular pressure and coronary flow hemodynamics, reduced oxidative damage, and restored the phosphorylation of survival proteins while inhibiting the p38 pathway, indicating the ability of Cs to prevent ischemic heart disease (Nader et al. 2016).

Research on Cs supplementation has demonstrated its ability to improve markers of cardiovascular health, such as lowering blood pressure, reducing inflammation, and improving lipid profiles. Additionally, Cs has been shown to have antiplatelet and antithrombotic effects, which may further contribute to its cardioprotective properties.

Overall, the antioxidant properties of Cs make it a promising natural remedy for managing cardiovascular disorders and preventing their progression. A brief description of the antioxidant characteristics of Cs extracts on cardiovascular disorders is provided in Table 3.

Table 3. Antioxidant effects of Crocus sativus extracts and essential oil in the cardiovascular disorders

Type of study	Experimental model	Dose, Duration	Effect	Ref.
In vivo studies	Normotensive and DOCA-induced hypertensive rats	2.5-10 mg/kg Intravenously	↓MABP ↓Oxidative stress associated with hypertension	(Imenshahidi et al. 2010)
	ISO-induced myocardial injury in male Wistar rats	100 mg/kg 7 days Orally	↓MDA ↑GPX Stabilized SOD activities Protection against oxidative damage	(Joukar et al. 2010)
	ISO-induced myocardial injury in male Wistar rats	200-800 mg/kg 30 days Orally	↓TBARS ↑SOD and CAT	(Sachdeva et al. 2012)
	DOX-induced cardiotoxicity in isolated rabbit hearts with IRI	10 µg/ml During reperfusion or 5 minutes before ischemia	↓Oxidative myocardial damage, p38 MAPK ↑Akt/mTOR/4EBP1 pathway activation	(Chahine et al. 2014)
	IRI in rabbit hearts	2 g/400 ml 6 weeks Orally	↓ LP, oxidative damage, p38 activity ↑GPx activity,Akt and 4EBP1 phosphorylation	(Nader et al. 2016)

Abbreviations: DOCA: Deoxycorticosterone acetate, MABP: mean arterial blood pressure, ISO: isoproterenol, MDA: Malondialdehyde, GPx: Glutathione peroxidase, TBARS: thiobarbituric acid-reactive substance, DOX: doxorubicin, IRI: ischemia/reperfusion injury, p38 MAPK: p38 mitogen-activated protein kinase, Akt: Ak strain transforming, mTOR: mammalian target of rapamycin, 4EBP1: 4E-binding protein 1, ApoE(-/-): apolipoprotein E, NT: Nitrotyrosine, Nrf2: nuclear erythroid 2-related factor, HO-1: heme oxygenase 1, MnSOD: manganese superoxide dismutase, eNOS: endothelial nitric oxide synthase.

Cancer and neoplasia

The antioxidant characteristics of Cs play a significant role in its potential as a chemo-preventive agent in cancer. These compounds exhibit various mechanisms that contribute to their anticancer effects, making Cs a potent candidate for cancer prevention and treatment. Cs extracts significantly decrease lipid peroxidation (LP) and enhance antioxidant levels, thereby reducing oxidative stress, which is a key factor in cancer development.

In vivo studies demonstrated that Cs aqueous extracts significantly reduced tumor volume and increased the lifespan of cancer-bearing mice (Mohammed, Tousson and Yassin 2020). The prevention of aqueous extract of Cs on skin cancer development in mice induced by chemicals, when given orally prior and post to cancer induction, Cs hindered the development of skin papillomas and shrank their size. The antioxidant enzymes in liver tissue samples were also assessed, showing a beneficial action of Cs. Overall, Cs was found to inhibit 1,2-dimethylbenz[a]anthracene (DMBA)-induced skin carcinoma in mice, potentially due to the induction of cellular defense systems (Das and Saha 2010).

The chemopreventive effect of Cs aqueous extract against diethylnitrosamine (DEN)-induced liver cancer in male Wistar rats demonstrated that Cs administration (75, 150 and 300 mg/kg/day, orally, during two weeks prior to administration of DEN) produced a significant reduction in liver nodule formation and GST-positive foci. Oxidative stress was also decreased by Cs, by increasing antioxidant enzymes activity, but reduction cell proliferation marker and mediators of inflammation suppressed, and the liver cells induced apoptosis (Amin et al. 2011). In a Wistar albino rat model exposed to N-methyl-N’-nitro-N-nitrosoguanidine (MNNG), the potential effects of Cs (respectively 100, 150, and 175 mg/kg SAE for 50 days, intra peritoneal) in a controlled laboratory environment were investigated. Cs inhibited the progression of gastric cancer in rats in a dose-dependent manner (Bathaie et al. 2013). The preventive effect of Cs on oral squamous cell carcinogenesis in Syrian golden hamsters induced by DMBA showed that (100 mg/kg body weight/day, orally) did not develop tumors but showed hyperplasia and dysplasia. Cs also restored detoxification enzymes and antioxidant levels, suggesting its chemo-preventive effects through antioxidant characteristics and detoxification modulation (Manoharan et al. 2013).

Activation of the Nrf2 signaling pathway by the Cs serves as a defense mechanism against oxidative stress and inflammation, two factors associated with carcinogenesis (Khoshandam, Razavi and Hosseinzadeh 2022). The Cs extract demonstrated robust antioxidant characteristics that could potentially safeguard cells against oxidative harm and inhibit cancer progression. Additionally, Cs with anti-inflammatory and anti-proliferative effects may have a crucial role in targeting cancer cells, suggesting its potential as a promising therapy for cancer (Hosseinzadeh 2019).

Findings from an experiment focusing on how high-intensity interval training (HIIT) and SAE oral supplementation affected skeletal muscle in cancer-afflicted mice with cachexia showed that Cs extract alone, without HIIT, possessed antioxidants and minimized muscle apoptosis. Cs achieved protection against apoptosis in skeletal muscle through the enhancement of antioxidant defense, as indicated by decreased pro-apoptotic and increased anti-apoptotic markers (Ahmadabadi et al. 2020).

The ability of Cs to neutralize free radicals and decrease oxidative stress, a significant factor in the advancement of cancer has been demonstrated. Findings from animal studies have shown that Cs can effectively impede tumor growth and enhance survival rates for individuals with cancer. A study on mice demonstrated that Cs extract reduced tumor incidence and size in a dose-dependent manner. The antioxidant characteristics of Cs boosted the immune response against cancer cells, resulting in better treatment outcomes for different types of cancer. These results indicate that Cs could be a compound with significant therapeutic potential for a new, safe, and effective anticancer therapy. A brief description of the antioxidant characteristics of Cs extracts on cancer and neoplasia is provided in Table 4.

Table 4. Antioxidant effects of Crocus sativus extracts and essential oil in the cancer and neoplasia

Type of study	Experimental model	Dose, Duration	Effect	Ref.
In vivo studies	Swiss albino female mice	200 mg/kg 12 weeks Orally	↓Papilloma formation,Size of papillomas	(Das and Saha 2010)
	DEN induced rats	75-300 mg/kg 22 weeks Orally	↓Oxidative stress, oxidative damage ↑Antioxidant capacity Liver protection	(Amin et al. 2011b)
	MNNG-induced gastric cancer	100-175 mg/kg 50 days i.p	↓Cancer progression Antioxidant activity	(Bathaie et al. 2013)
	DMBA-induced buccal pouch carcinogenesis	100 mg/kg Starting 1day before DMBA exposure for 16 weeks Orally	↓Tumor formation Antioxidant activity, Detoxification modulation ↓LP	(Manoharan et al. 2013)
	4T1 cell line	200 mg/kg Thrice a week 4 weeks Orally	↓Caspase-3, Bax ↑Bcl-2, Bcl-2/Bax ratio All in SAE group	(Ahmadabadi et al. 2020)

Abbreviation: DEN: diethylnitrosamine, MNNG: N-methyl-N'-nitro-N-nitrosoguanidine, DMBA: 7,12-dimethylbenz[a]anthracene, BALB/c: Bagg Albino mice, 4T1: breast cancer cell line, Caspase-3: cysteine-aspartic acid protease, SAE: saffron aqueous extract, Bcl-2: B-cell lymphoma protein 2, Bax: Bcl-2-associated X protein.

Endocrine and metabolic disorders:

The antioxidant potential of Cs (25, 50, and 100 mg/kg) or crocin (4.84, 9.69, and 19.38 mg/kg) orally for 5 days in hyperlipidemic Wistar rats showed that both Cs and crocin increased antioxidant enzyme activity and reduced oxidative stress markers in the liver. Cs demonstrated a stronger antioxidant effect than crocin, indicating that other components in *Cs* may enhance its efficacy in combating oxidative damage in hyperlipidemia (Asdaq and Inamdar 2010). Hyperglycemic rats were analyzed for their response to Cs powder (0.08%, orally) and Cs-enriched rye bread (0.12% Cs, orally) in terms of their anti-diabetic effects. Significant improvements were observed in fasting glucose levels and glycemic control, along with decreased TBARS and triglyceride (TG) levels due to Cs and rye bread treatments and Cs alone was more effective than Cs-enriched rye bread in improving metabolic markers (Bajerska et al. 2013). Cs aqueous extract as an antioxidant (20, 40, and 80 mg/kg over 28 days, intraperitoneal) in Wistar rats with diabetes, increased levels of GSH, SOD, and CAT in hippocampus tissue, while also reducing blood glucose levels and advanced glycation end products (AGEs). This suggests that Cs extract could be beneficial in managing oxidative stress associated with diabetic encephalopathy (Samarghandian et al. 2014).

The Wistar rats were divided into control, streptozotocin (STZ, 40 mg/kg body weight), and STZ+Cs groups for the study of Cs on nonalcoholic fatty liver disease (NAFLD) in diabetic rats. Cs aqueous extract supplementation (100 mg/kg/day, orally) reduced blood glucose levels and liver steatosis in diabetic rats, highlighting its antioxidant characteristics and potential benefits for liver health. (Konstantopoulos et al. 2017). The antioxidant effects of Cs aqueous extract in diabetic rats were examined in 45 male Wistar rats divided into control, diabetic, and three Cs extract-treated groups, 10, 20, and 40 mg/kg/day, administered intraperitoneally (i.p.) for four weeks, starting three days after inducing diabetes. The rats treated with Cs exhibited notable decreases in oxidative stress indicators and higher levels of antioxidant enzyme functions in a manner that depended on the dosage. This study highlights Cs potential in reducing diabetes-induced oxidative damage (Samarghandian et al. 2017). The antioxidant effects of Cs in ApoE knockout (ApoE-/-) mice, a model for atherosclerosis, on a high-fat diet were examined in mice treated with SAE at doses of 30, 60, and 90 mg/kg/day orally for four weeks. Cs significantly reduced oxidative stress in atherosclerotic plaques and enhanced antioxidant defenses, thereby stabilizing plaque formation (Christodoulou et al. 2018).

Cs as an antioxidant (25 mg/kg/day, orally) on oxidative stress and retinal damage in ApoE-/- mice fed a high-fat diet reduced oxidative stress and preserved retinal thickness, suggesting its potential as an antioxidant for protecting retinal tissue damage (Doumouchtsis et al. 2018). Cs aqueous extract (100 mg/kg, orally) and metformin for six weeks in glucose, lipids, and pancreatic tissue were investigated in STZ-induced diabetic rats, decreasing blood glucose and cholesterol levels, improving insulin levels, and repairing pancreatic tissue damage. This suggests that Cs may have antioxidant and therapeutic effects in managing diabetes (Jiang et al. 2018). Hydroalcoholic Cs extract (500 mg/kg, for three weeks, intraperitoneal) in an STZ-induced mouse model (C57BL/6) of autoimmune diabetes, reduced blood glucose levels, improved insulin secretion, and decreased inflammation. The results suggest that Cs extract has antioxidant effects that may protect pancreatic cells and support diabetes management (Faridi, Delirezh and Abtahi Froushani 2019). The Cs aqueous extract on the retinas of STZ-induced diabetic Wistar rats, reduced antioxidant enzyme activities and increased malondialdehyde (MDA) levels, but Cs (60 mg/kg every other day, intraperitoneal) for ten weeks of treatment significantly increased SOD and GPx activities and decreased MDA levels in diabetic rats. This suggests that Cs extract may have a protective antioxidant effect in diabetic rat retinas, potentially reducing oxidative stress linked to diabetic retinopathy (Skourtis et al. 2020). Cs effects on diabetic nephropathy in type 1 diabetic rats were examined by focusing on its ability to regulate the expression of connective tissue growth factor (CTGF), receptor for advanced glycation end products (RAGE) genes, and its impact on oxidative stress. In 24 male Wistar rats with diabetes induced using STZ, Cs hydroalcoholic extract was administered at doses of 20 and 40 mg/kg, intraperitoneally for 42 days. Cs treatment improved serum levels and gene expression, suggesting it may be beneficial in preventing and treating diabetic nephropathy (Amri et al. 2021). In another study with STZ-induced diabetic Wistar rats, a 60 mg/kg dose of Cs aqueous extract (orally) over ten weeks increased activities of SOD and GPx and significantly decreased MDA levels, indicating effective antioxidant protection in the retina. These findings collectively highlight Cs's potential as an antioxidant in various models of diabetes (Ahmad et al. 2022).

The impacts of saffron petal extract (SPE, 50, 200, and 600 mg/kg, intraperitoneal) and saffron petal anthocyanins (SPA, 20, 40, and 80 mg/kg, intraperitoneal) for two weeks on ovarian function and oxidative stress in a mouse model (BALB/c) of polycystic ovary syndrome (PCOS) induced by testosterone enanthate (TE) were explored. Both SPE and SPA increased antioxidant enzymes in ovarian tissues and showed antioxidant activity in various assays, suggesting their potential in treating oxidative stress-related disorders in PCOS (Moshfegh et al. 2022).

Studies have shown that Cs may help to regulate hormone levels in the body, as well as improve the body's ability to metabolize nutrients. This could make it an effective treatment for conditions such as diabetes and thyroid disorders, which are characterized by hormone imbalances and impaired metabolism. Furthermore, studies have demonstrated that Cs possesses anti-inflammatory characteristics that could potentially decrease inflammation and enhance overall well-being. In general, the antioxidant qualities of Cs show great potential for treating endocrine and metabolic disorders. This natural remedy could serve as a viable and effective alternative to conventional pharmaceutical treatments. A brief description of the antioxidant characteristics of Cs extracts on endocrine and metabolic disorders is provided in Table 5.

Gastrointestinal and liver disorders

The influence of Cs aqueous extract on liver disorders in mice exposed to aluminum chloride (AlCl3) showed that Cs (200 mg/day for 45 days, orally) treatment reduced LP levels and improved liver function markers. This suggests that Cs has antioxidant characteristics that can enhance liver health (Shati and Alamri 2010). Another study used saffron ethanolic extract (SEE) orally for experimenting on protection against liver damage caused by I/R injury in Sprague-Dawley rats. Pretreatment with SEE significantly reduced intracellular ROS levels and increased the activity of antioxidant enzymes like SOD1 and CAT. In addition, SEE significantly reduced cell apoptosis compared to I/R samples. These results highlight SEE's potential as a therapeutic agent for conditions involving ROS-induced liver damage (Pan et al. 2013). The hepato-protective potential of a SPE against acetaminophen-induced liver damage in male Wistar rats showed that the intraperitoneal Cs aqueous extract at doses of 10 and 20 mg/kg significantly decreased liver enzyme and bilirubin levels while increasing total protein and albumin levels. Cs can help to scavenge free radicals and reduce oxidative stress in the liver. Histopathological examinations revealed protective effects of the Cs extract, including reduced inflammation and necrosis in the liver (Omidi et al. 2014). The protective effects of Cs aqueous extract on liver tissue in high-fat diet-induced obese rats showed that Cs extract, at both 40 and 80 mg/kg doses, significantly reduced liver enzyme levels and improved liver histopathology in obese rats compared to the control, indicating a dose-dependent hepatoprotective effect (Mashmoul et al. 2016).

The protective effects of the hydroalcoholic extract of the petals of Cs on inflammatory and enzymatic indices in the liver and kidneys of male Wistar rats exposed to alcohol showed that Cs extract (167.5 or 335 mg/kg/day for either eight weeks, orally), significantly reduced the serum concentration of inflammatory indicators, kidney enzymes, and liver enzymes in all treated groups compared to the control group (Azizi et al. 2019). In male Wistar rats, Cs aqueous extract protected against liver damage induced by methotrexate (MTX). The results showed that MTX led to an increase in liver enzyme and oxidative stress marker levels, but when Cs extract was administered (at a dose of 80 mg/kg for 10 days, starting three days before MTX, intraperitoneal), oxidative stress and liver morphology were improved. Pre-and-post-treatment with Cs extract showed better protective effects compared to post-treatment alone (Hoshyar et al. 2019). The protective effect of Cs aqueous extract against ethanol-induced oxidative stress and tissue damage in male Wistar rats were done by administration of Cs extract (40, 80, and 160 mg/kg, orally) along with ethanol for four weeks. Cs extract restored levels of MDA and GSH, reduced pro-inflammatory cytokines, and inhibited apoptosis in the kidney and liver. Histo-pathological evaluations demonstrated that Cs extract alleviated ethanol-induced tissue damage, highlighting its antioxidant, anti-apoptotic, and anti-inflammatory properties (Rezaee-Khorasany et al. 2019). Copper nanoparticles (CuNPs) induced oxidative stress and liver injury in male albino mice, but treatment with oral SEE at a dose of 60 mg/kg showed protective effects against the liver injury. SEE improved survival rates, oxidative stress markers, and DNA integrity, suggesting that Cs and its active compounds, particularly crocin, could serve as natural antioxidants to prevent liver damage from CuNPs (Attia et al. 2021).

Administering 10 and 20 mg/kg, doses of SAE orally for four days prior to inducing colitis in a murine model with dextran sulfate sodium (DSS) significantly improved the histopathological characteristics of the colon and decreased the secretion of pro-inflammatory cytokines. Additionally, Cs influenced the gut microbiota composition and boosted the levels of beneficial short-chain fatty acids (SCFAs), indicating its potential role in mitigating inflammation effects in the gastrointestinal tract (Banskota et al. 2021). Administering a hydroalcoholic extract of Cs (0.09 g/kg/day for six weeks, orally) to Zucker diabetic fatty rats, improved hyperglycemia and modulated gut microbiota dysbiosis. Occludin expression increased, levels of lipopolysaccharide (LPS) and inflammatory markers reduced, and the insulin signaling pathway enhanced while glycerolipid and fatty acid metabolism were inhibited in the liver (Li et al. 2021). Administering Cs aqueous extract at a dose of 20 mg/kg, orally improved inflammation in a colitis model using C57BL/6 mice. The treatment resulted in better colon health, reduced disease activity, and changes immune cell populations. Cs also increased protein expression, which is associated with anti-inflammatory pathways (Singh et al. 2022). The impact of Cs hydroalcoholic extract on hepatic inflammation and fibrosis in male C57BL/6 mice induced by carbon tetrachloride (CCl4) injections was explored by giving daily doses of Cs at 10 and 20 mg/kg, orally for four weeks. The results showed significant improvements in liver function and a reduction in liver inflammation and fibrosis in a dose-dependent manner. These findings suggest that Cs provides protective effects against liver damage and fibrosis through its antioxidant characteristics (Huang et al. 2023). Using a liver fibrosis model induced by CCl4 in kunming mice (KM), the pharmacological influence of Cs extract was examined by administration of SAE at daily doses of 50 and 100 mg/kg, orally for six weeks. Cs treatment, substantially improved liver fibrosis by lowering levels of important inflammatory and fibrotic markers including hypoxia-inducible factor-1 (HIF-1), vascular endothelial growth factor A (VEGFA), Akt, and phosphoinositide 3-kinase (PI3K). By utilizing its antioxidant characteristics, Cs may offer protective benefits against liver fibrosis, suggesting it could regulate crucial signaling pathways (Jiang et al. 2023). Oral Cs aqueous extract on colitis in a C57BL/6 mouse model induced by DSS, maintained gut microbiota balance and reduced pro-inflammatory bacteria. These findings suggest that Cs may have therapeutic potential in alleviating the effects of inflammatory bowel disease (IBD) by modulating the gut microbiome and related metabolic changes (Singh et al. 2023).

Studies have shown that Cs supplementation alleviates symptoms of gastrointestinal damage by reducing inflammation and oxidative stress in the gut lining. Additionally, the antioxidant characteristics of Cs may also help promote gut health by maintaining a healthy balance of gut bacteria. Moreover, research has suggested that Cs may be a promising natural alternative for individuals suffering from gastrointestinal conditions. By including Cs in the diet or taking Cs supplements, individuals may be able to support the health of their gut and reduce the risk of gastrointestinal damage. Further studies are needed to fully understand the mechanisms by which Cs exerts its protective effects on the gastrointestinal tract, but the existing evidence suggests that Cs may be a valuable tool in promoting gut and liver health and preventing gastrointestinal damage. A brief description of the antioxidant characteristics of Cs extracts on gastrointestinal and liver disorders is provided in Table 6.

General health

Adding saffron waste (SW) to the diet of male lambs at a daily dose of 60 g for 30 days resulted in notable antioxidant effects. This included a decrease in MDA levels, an increase in total antioxidant capacity (TAC), and a reduction in cholesterol levels when compared to the control group. These findings suggest that adding Cs waste to the diet may enhance the antioxidant status and positively influence the health indicators of lambs (Kazemi 2024). Administering 30 mg/kg of Cs extract via injection (i.p.) during chronic restraint stress in Wistar rats notably decreased MDA levels, indicating reduced LP, and boosted the activities of antioxidant enzymes. These findings suggest that Cs can mitigate oxidative stress damage across various organs (Bandegi et al. 2014).

Immunological and autoimmune disorders

Administering oral Cs aqueous extract to sensitized guinea pigs reduced tracheal responsiveness (TR) and inflammatory mediators in the blood. The *Cs* extract increased interferon gamma (IFN-γ) levels and improved the T helper type 1/T helper type 2 (Th1/Th2) balance. The highest concentration of Cs extract was more effective than lower concentrations and dexamethasone in preventing inflammatory responses in allergic conditions (Byrami et al. 2013).

Table 5. Antioxidant effects of *Crocus sativus* extracts and essential oil in the endocrine and metabolic disorders

Type of study	Experimental model	Dose, Duration	Effect	Ref.
In vivo studies	Hyperlipidemic	25-100 mg/kg 5 days	↑SOD, CAT, FRAP, SH ↓MDA ↓TBARS in liver tissue	(Asdaq and Inamdar 2010)
	STZ-induced hyperglycemic	0.08% in high-fat diet 5 weeks	↓FBS (47% ↓vs. HF/STZ; p<.05)	(Bajerska et al. 2013)
		0.12% in high-fat diet for 5 weeks	↓FBS (53% ↓vs. HF/STZ; p<.05)	
	STZ-induced diabetic	20-80 mg/kg 28 days	↑GSH, SOD, CAT, AGEs ↓BG	(Samarghandian et al. 2014)
		40 mg/kg/day 6 weeks	↑Insulin release,glucose uptake ↓Serum glucose	(Dehghan et al. 2016)
		100 mg/kg/day 8 weeks	↓Serum glucose levels,Liver steatosis Hepatoprotective Hypoglycemic effects	(Konstantopoulos et al. 2017)
		100 mg/kg/day 6 weeks	↓BG, blood lipids Improvement of pancreatic tissue	(Jiang et al. 2018)
		500 mg/kg/day 3 weeks	↓BG,Pro-inflammatory cytokines ↑Insulin secretion	(Faridi et al. 2019)
		60 mg/kg Every other day 10 weeks	↑SOD, GPx, CAT ↓MDA levels	(Skourtis et al. 2020)
		20, 40 mg/kg/day 6 weeks	↑SOD activity ↓MDA levels,CTGF and RAGE gene expression	(Amri et al. 2021)
		60 mg/kg 10 weeks	↑SOD and GPx activities ↓MDA levels Antioxidant protection in retina	(Ahmad et al. 2022)
	ApoE knockout (ApoE-/-) mice fed high-fat diet	30-90 mg/kg/day 4 weeks	↓Oxidative stress ↑Antioxidant defenses	(Christodoulou et al. 2018)
		25 mg/kg/day 20 weeks	↓Oxidative stress Preservation of retinal thickness	(Doumouchtsis et al. 2018)
	TE induced PCOS	SPE (50, 200, 600 mg/kg/day) SPA (20, 40, 80 mg/kg) 2 weeks	↑ GPx, SOD, CAT, GST, GSH	(Moshfegh et al. 2022)

Abbreviation: ApoE(-/-): apolipoprotein E, FRAP: ferric ion reducing antioxidant power, SH: sulfhydryl group, STZ: Streptozocin or Streptozotocin, FBS: fasting blood sugar, HF/STZ: the streptozotocin-high fat diet, BG: Blood glucose, AGEs: advanced glycation end products, NO: nitric oxide, C57BL/6: C57 black 6, CTGF: connective tissue growth factor, RAGE: receptor for advanced glycation endproducts, SPE: saffron petal extract, SPA: saffron petal anthocyanins, PCOS: polycystic ovary syndrome, TE: testosterone enanthate, GST: glutathione S-transferase, GGT: gamma-glutamyl transpeptidase, SOD: superoxide dismutase, CAT: catalase, GSH: glutathione, MDA: Malondialdehyde, GPx: Glutathione peroxidase, TBARS: thiobarbituric acid-reactive substance.

Table 6. Antioxidant effects of *Crocus sativus* extracts and essential oil in the gastrointestinal and liver disorders

Type of study	Experimental model	Dose, Duration	Effect	Ref.
In vivo studies	BALB/c and C57BL/6 mice	200 mg/kg/day 45 days	↓LP Improved GGT, ALT, AST, ALP	(Shati and Alamri 2010)
	Rat model of hepatic IRI	Not specified	↓Intracellular ROS, Cell apoptosis ↑SOD1 and CAT levels	(Pan et al. 2013)
	Pregnant BALB/c mice (neonates)	500-2000 mg/kg/day 21 days	No toxic effect on liver Histopathological changes in kidneys	(Bahmani et al. 2014)
	Male Wistar rats	10, 20 mg/kg 6 days	↓ALT, AST, and necrosis and inflammation	(Omidi et al. 2014)
	Male Sprague Dawley rats fed a high-fat diet	40,80 mg/kg 8 weeks	↓Liver enzyme levels (AST, ALT, ALP) Improved liver histopathology	(Mashmoul et al. 2016)
		167.5, 335 mg/kg/day 8 weeks	↓Inflammatory indicators, Renal enzymes, and Hepatic enzymes	(Azizi et al. 2019)
	Male Wistar rats	80 mg/kg 10 days	↓Liver enzymes (AST, ALT, ALP)n SOD activity ↓Oxidative stress markers (MDA, NO) Improved liver histology	(Hoshyar et al. 2019)
		40-160 mg/kg 4 weeks Orally	↓MDA, Caspase-3, -8, -9, Bax/Bcl2 ratio ↑GSH Improved histopathology of liver and kidneys	(Rezaee-Khorasany et al. 2019)
	Adult male albino mice	60 mg/kg 30 days	↓Hepatotoxicity Improved oxidative stress markers Preserved DNA integrity Protective against liver damage	(Attia et al. 2021)
	DSS-induced colitis	10, 20 mg/kg 4 days	Improved histopathological characteristiCs Modulated gut microbiota ↑SCFAs	(Banskota et al. 2021)
	ZDF rats	0.09 g/kg/day, 6 weeks	↑Insulin signaling ↓Glycerolipid and fatty acid metabolism	(Li et al. 2021)
	DSS-induced colitis	20 mg/kg, 9 days	↓DAI, M1 ↑M2, IL-10+ dendritic cells, CD3+ T and CD3+ CD8+ T cells, CD25+ T cells, FoxP3+ CD25+ regulatory T cells, HO-1 and GPx2 protein expression	(Singh et al. 2022)
		20 mg/kg,10 days	↓Pro-inflammatory bacteria ↑F/B ratio Alterations in uric acid, cholesterol, 2-hydroxyglutaric acid, allantoic acid	(Singh et al. 2023)
	CCl4-induced hepatic fibrosis	10-20 mg/kg 4 weeks	↑Liver function ↓Liver inflammation	(Huang et al. 2023)
	CCl4 -induced liver fibrosis	50-100 mg/kg 6 weeks	↓Liver fibrosis, HIF-1, VEGFA, Akt, PI3K	(Jiang et al. 2023)
	Stress induced oxidative damage in Rats	30 mg/kg 21 days, i.p	↓MDA levels, activities of GPx, GSR, and SOD ↑TAR	(Bandegi et al. 2014)

Abbreviation:LP: lipid peroxidation, GGT: gamma-glutamyl transpeptidase , ALT: alanine aminotransferase , AST, ALP: aspartate aminotransferase, ROS: oxygen species, SOD: superoxide dismutase,CAT: catalase, MDA: malondialdehyde,NO: nitric oxide,SOD: superoxide dismutase,GSH: glutathione,Bax: Bcl-2-associated X protein, Bcl-2: B-cell lymphoma protein 2,SCFAs: short-chain fatty acids,DAI: disease activity index,M1: pro-inflammatory macrophages, M2: anti-inflammatory macrophages FoxP3+: FoxP3: forkhead box P3,HO-1: HO-1: heme oxygenase 1,GPx2: Glutathione peroxidase 2,Nrf-2: Nrf2: nuclear erythroid 2-related factor ,HIF-1: hypoxia-inducible factor-1,VEGFA: vascular endothelial growth factor A, Akt: Ak strain transforming I3K,TAR: TAR: total antioxidant reactivity,GSR: glutathione reductase, CCl4: carbon tetrachloride. CD3: cluster of differentiation 3, 8.

Neurologic disorders

The impact of Cs aqueous and ethanolic extracts given through intraperitoneal at doses of 50, 100, and 200 mg/kg/day for a period of 7 days on neuropathic pain caused by chronic constriction injury in Wistar rats was explored. The results from behavioral assessments indicated a significant, dose-dependent reduction in neuropathic pain symptoms, such as thermal hyperalgesia and mechanical allodynia. The Cs-treated groups showed pain reduction similar to that seen for gabapentin-treated group. These findings suggest that Cs extracts might offer therapeutic benefits as complementary treatments for neuropathic pain (Amin and Hosseinzadeh 2012). The effects of Cs aqueous extract (250 mg/kg, intraperitoneal) on vascular cognitive impairment were examined in a Wistar rat model of chronic cerebral hypoperfusion. After permanently occluding the common carotid arteries, rats were given doses of Cs extract for 5 days. The results indicated that Cs extract significantly enhanced cognitive outcomes. These findings suggest that the antioxidant characteristics of Cs extract may help preserve cognitive functions following cerebral ischemia (Hosseinzadeh et al. 2012). In a study involving male adult BALB/c mice, the antioxidant effects of Cs hydroalcoholic extract (60 mg/kg/day i.p) were assessed against neurotoxicity caused by AlCl3 (50 mg/kg/day, for five weeks). The results showed a reduction in LP, as evidenced by lower MDA levels, and an increase in GSH level in the brain. These findings suggest that Cs has protective antioxidant effects *in vivo* against aluminum-induced toxicity (Linardaki et al. 2013). In an experiment with male Wistar rats, the effects of Cs aqueous and ethanlic extract as antioxidants were studied in a chronic constriction injury (CCI) model. The findings revealed that Cs extract (200 mg/kg for seven consecutive days, intraperitoneal) significantly decreased MDA levels, a marker of oxidative stress, and increased GSH levels in CCI animals. These results demonstrate the antioxidant activity of Cs extracts in alleviating oxidative stress associated with neuropathic pain (Amin et al. 2014).

The antioxidant characteristics of the aqueous extract from the stigma of Cs (50, 100, and 200 mg/kg, three times per week for four weeks, i.p.) in male Wistar rats treated with diazinon (DZN) were done. The results showed that Cs extract significantly inhibited the increase of markers of oxidative stress, which indicates neuronal damage. These findings suggest the protective effects of Cs against oxidative damage induced by DZN (Moallem et al. 2014). The antioxidant characteristic SME of Cs was conducted using a Drosophila melanogaster model exposed to rotenone-induced oxidative stress by oral administration of SME at doses of 0.05% and 0.1% for seven days. The findings revealed that SME notably boosted levels of GSH and total sulphydryl groups (TSH) and enhanced activities of antioxidant enzymes. Moreover, SME effectively diminished markers of oxidative stress, suggesting its protective role against rotenone-induced oxidative damage in this model (Rao et al. 2016). The effects of a hydroalcoholic extract from Cs (given a diet enriched with Cs extract, 50 mg/kg per day for a month) on antioxidant activity in 5XFAD mice, a model of AD, were explored. Cs extract, reduced Aβ load, decreased neuroinflammation, improved blood-brain barrier (BBB) integrity, and increased levels of synaptic proteins in the brains of the treated mice. These findings suggest that Cs extract may help mitigate oxidative stress-related pathological changes associated with AD (Batarseh et al. 2017b). The effects of Cs aqueous extract, in enhancing neuroprotection and antioxidant activity in Wistar rats with cerebral I/R injury was performed by giving Cs extract at doses of 100 or 200 mg/kg, i.p for three weeks prior to inducing I/R in the left brain, with additional doses around the time of surgery. Treatment with Cs significantly lowered lipid peroxidation (LP), nitric oxide (NO), and brain natriuretic peptide (BNP) in the brain tissue, while increasing GSH, thus reducing oxidative stress. Moreover, Cs reduced apoptotic markers like caspase-3 and Bax, and increased the expression of VEGF, emphasizing its potential as an antioxidant and neuro-protective agent against cerebral I/R injury (Abdel-Rahman et al. 2020). The potential antioxidant benefits of oral SAE were examined in Drosophila models of PD with mutated α-synuclein A30P and G51D. *Cs* significantly improved climbing ability and increased the lifespan of flies in the G51D PD model, demonstrating its potential antioxidant benefits in alleviating PD-related symptoms (Inoue et al. 2021). Cs antioxidant characteristics were evaluated in zebrafish with traumatic brain injuries (TBI). Zebrafish were given (i.p.) injections of Cs hydro-methanolic extract (50 mg/kg) for five days. The results revealed that Cs treatment significantly improved memory performance, reduced anxiety-like behaviors, and enhanced learning abilities in the zebrafish, indicating its potential antioxidant and neuro-protective benefits following TBI (Chaoul et al. 2022). The exploration of Cs (50 mg/kg i.p, over 14 days) antioxidant characteristics in a repetitive mild traumatic brain injury model utilized male BALB/c indicated that treatment with Cs notably decreased oxidative stress and markers of inflammation in the brain, suggesting that it has a neuro-protective effect in the rmTBI mouse model (Salem et al. 2022).

The effects of standardized Cs hydro-alcoholic extract on cognitive decline and neuroinflammation in chronically scopolamine-treated Wistar rats were assessed. Rats were given varying doses of Cs extract (10, 15, and 20 mg/kg, orally) alongside scopolamine for four weeks, revealing that scopolamine impaired memory and caused brain abnormalities. However, Cs extract supplementation improved cognitive performance, reduced acetylcholinesterase (AChE) activity, and increased antioxidant levels. The highest dose of Cs extract notably decreased brain abnormalities and inflammation. Molecular docking studies supported these results, showing that trans-crocetin, a Cs component, had potent AChE inhibitory activity (Patel et al. 2024). An *in vivo* study showed that intraperitoneal Cs aqueous extract at 20 and 80 mg/kg doses was associated with a decrease in MDA and an increase in thiol, CAT, and SOD in the brain of Wistar rats exposed to paraquat (PQ). These findings highlight the neuroprotective role of Cs, in the management of neurological disorders caused by toxins such as PQ (Beigoli et al. 2024).

Several studies have highlighted the neuro-protective effects of Cs and its potential to improve cognitive function, memory, and mood in individuals with neurologic disorders. The antioxidant properties of Cs are thought to help combat the damaging effects of free radicals and reduce inflammation in the brain, ultimately leading to a decrease in neuro-degeneration and improved neurological function. A brief description of the antioxidant characteristics of Cs extracts on neurologic disorders is provided in Table 7.

Respiratory disorders

The influence of Cs hydro-ethanolic extract on TR and inflammatory mediators in sensitized guinea pigs were explored by giving the extract (20, 40, and 80 mg/kg/day, orally) during the sensitization period. The findings revealed a significant decrease in TR to methacholine and OVA, along with reductions in IL-4, total NO, and nitrite levels. Additionally, the extract boosted IFN-γ levels and enhanced the Th1/Th2 balance, with the highest concentration producing the most substantial effects, even exceeding those of dexamethasone (Byrami et al. 2013). The potential of Cs aqueous extract to protect against PQ-induced lung injury in Wistar rats was explored through an investigation into its antioxidant characteristics. Treatment with intraperitoneal Cs extract and pioglitazone improved lung function and antioxidant levels, with the combination therapy showing similar or better effects than dexamethasone. This suggests that Cs may be a promising treatment for lung injury when used in combination with pioglitazone (Memarzia et al. 2023).

The antioxidant power of intraperitoneal Cs aqueous extract was shown by its ability to boost antioxidant enzymes like SOD, CAT, and thiol compounds in the lung fluid of Wistar rats exposed to PQ indicating the effect of CS on the harmful oxidative stress caused by PQ, and protecting the lungs from oxidative injury (Memarzia et al. 2025).

In a study tracheal smooth muscle (TSM) of 54 male Wistar rats was contracted by methacholine or KCl, and the relaxant effects of different concentrations of aqueous-alcoholic extract of Cs petal (0.1, 0.2, 0.4 and 0.8 mg/ml), theophylline (0.2, 0.4, 0.6 and 0.8 mM) or 1 mL normal saline were tested. The results showed the concentration-dependent relaxant effects of Cs extract on TSM and suggests that the possible mechanisms are inhibition of histamine receptors and cyclooxygenase (COX) pathway. However, the relaxant effects of all concentrations were remarkably lower compared to those of theophylline (Behrouz et al. 2025).

Studies have shown that Cs can reduce inflammation in the lungs, improve lung function, and protect against oxidative stress, which can improve overall lung health in patients with pulmonary disorders. A brief description of the antioxidant characteristics of Cs extracts on respiratory disorders is provided in Table 8.

Table 7. Antioxidant effects of Crocus sativus extracts and essential oil in the neurologic disorders

Type of study	Experimental model	Dose, Duration	Effect	Ref.
In vivo studies	AlCl3-induced toxicity	60 mg/kg/day 5 week	↓MDA levels ↑GSH levels in the brain	(Linardaki et al. 2013)
	CCI model	200 mg/kg 7 days	↓MDA ↑GSH	(Amin et al. 2014)
	DZN-induced neuronal damage	50-200 mg/kg 3 times/week 4 weeks	↓Direct 8-iso-PGF2α (oxidative stress marker) ↓S100b (neuronal damage marker)	(Moallem et al. 2014)
	Rotenone-induced oxidative stress	SME 0.05% and 0.1% 7 days Orally	↑GSH and TSH levels, oxidative stress markers ↑Antioxidant enzyme activities	(Rao et al. 2016)
	1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) induced PD	14 mg/kg 5 days	↓Loss of dopaminergic cells in substantia nigra pars compacta ↓Abnormal neuronal activity in caudate-putamen complex	(Skladnev et al. 2016)
	5XFAD induced AD	50 mg/kg/day 1 month	↓Aβ load ↓Neuroinflammation ↑Synaptic proteins	(Batarseh et al. 2017a)
	Diet enriched with Cs	100, 200 mg/kg 3 weeks + four doses around surgery	↓LP, NO,BNP, apoptosis markers (caspase-3, Bax) ↑GSH, VEGF expression	(Abdel-Rahman et al. 2020)
	PD model in drosophila	3-30 µg/ml	↑Climbing ability ↑Lifespan in G51D model	(Inoue et al. 2021)
	Zebrafish- induced TBI	50 mg/kg, 5 days, i.p	↑Memory performance ↓Anxiety-like behaviors ↑Learning ability	(Chaoul et al. 2022)
	TBI model	50 mg/kg i.p,14 days	↓Oxidative stress, Inflammatory markers	(Salem et al. 2022)

Abbreviation: CCI: Chronic Constriction Injury, AlCl3: Aluminum, DZN: diazinon, 8-iso-PGF2α: 8-iso-prostaglandin F2α, SME: saffron methanolic extract, GSH: glutathione, TSH: total sulphydryl groups, Aβ: amyloid beta, BBB: blood-brain barrier, LP: lipid peroxidation, NO: nitric oxide, BNP: brain natriuretic peptide, GSH: glutathione, VEGFA: vascular endothelial growth factor A, TBI: traumatic brain injuries.

Table 8. Antioxidant effects of *Crocus sativus* extracts and essential oil in the respiratory and urogenital disorders

Type of study	Disorders	Experimental model	Dose, Duration	Effect	Ref.
In vivo studies	Respiratory disorders	OVA sensitized guinea-pigs	20, 80 mg/kg/day	↓ total NO, and nitrite ↑IFN-γ ↑Th1/Th2 balance	(Byrami et al. 2013)
		PQ-induced lung injury		↓Lung inflammation, oxidative stress, total and differential WBC counts ↑SOD, CAT, thiol levels	(Memarzia et al. 2023)
	Urogenital disorders	Gentamicin-induced nephrotoxicity	40,80 mg/kg/d 10 days,Orally	↑Antioxidant activity ↓MDA levels	(Ajami et al. 2010)
		AKI induced I/R	5-20 mg/kg 30 minutes before ischemia i.p.	↓Plasma creatinine, ↓MDA levels ↑ FRAP level	(Mahmoudzadeh et al. 2017)
		HUA	High, medium, and low doses; duration not specified	↓Serum uric acid levels (all groups) ↓Urine uric acid levels (high-dose group) ↓XOD protein and mRNA expression (positive drug and NMPCS groups)	(Li et al. 2022)

Abbreviations: Ref: references, OVA: Ovalbumin, PQ: paraquat, AKI: acute kidney injury, HUA: hyperuricemia, MDA: Malondialdehyde, NO: nitric oxide, SOD: superoxide dismutase, CAT: catalase, FRAP: ferric ion reducing antioxidant power, XOD: xanthine oxidase, NMPCS: novel medicinal components of *Crocus sativus,* Th1: T helper type 1, Th2: T helper type 2.

Urogenital disorders

The impact of Cs aqueous extract on gentamicin-induced nephrotoxicity in male Wistar rats, which received either Cs aqueous extract in conjunction with gentamicin. Cs treatment at 80 mg/kg, i.p significantly reduced oxidative damage in the kidneys, by reduced level of MDA (Ajami et al. 2010). The *in vivo* antioxidant capability of Cs aqueous extract (5, 10, and 20 mg/kg, i.p) in a Wistar rat model of acute kidney injury (AKI) induced by I/R was evaluated. The treatment significantly lowered plasma creatinine and MDA levels, indicating reduced oxidative stress. Furthermore, the antioxidant capacity, as assessed by the FRAP, increased and matched the levels observed in the control group. These results imply that Cs extract has substantial antioxidant characteristics that can mitigate oxidative damage in renal tissue during I/R injury (Mahmoudzadeh et al. 2017). In a rat model of hyperuricemia (HUA), granules made from components of Cs possess antioxidant characteristics. Treatment with oral Cs at various doses reduced serum uric acid level and xanthine oxidase (XOD) activity, suggesting its potential as a therapeutic agent for HUA (Li et al. 2022). A brief description of the antioxidant characteristics of Cs extracts on urogenital disorders is provided in Table 8.

Clinical studies

The clinical significance of antioxidant characteristics in Cs extracts is underscored by their potential therapeutic effects in various health conditions, particularly those involving oxidative stress.

Endocrine and metabolic disorders

Cs intake may improve glycemic and antioxidant indices in this population (Kermani et al. 2015). The effect of Cs supplementation (Tables 100 mg/day) on type 2 diabetes mellitus (T2DM) patients showed that after 12 weeks of Cs supplementation, diabetic patients displayed favorable changes in waist circumference (WC) and serum MDA levels, though no significant impact was observed on other cardiovascular risk factors (Ebrahimi et al. 2019). In a clinical study, Cs extract (15 mg/day) reduced HbA1c, FBS, and enhanced the DPPH radical scavenging activity in overweight/obese pre-diabetic participants. Hence, Cs may enhance glycemic and antioxidant levels and is advised for individuals at risk for developing diabetes. Despite this, the addition of Cs did not have an impact on lipid levels (Karimi-Nazari et al. 2019).

In a randomized controlled trial (RCT), treatment with Cs supplementation (100 mg/day, for 8 weeks) in patients with T2DM decreased FBS, lipid profile, atherogenic indices, and liver enzyme serum levels. Additionally, NO and MDA were reduced; thus, Cs supplementation may be considered useful for T2DM patients (Tajaddini et al. 2023).

The above clinical studies suggest potential benefits of Cs in managing endocrine and metabolic disorders, especially by improving glycemic control and antioxidant status in individuals with pre-diabetes and T2DM. Cs supplementation has been shown to reduce FBS, HbA1c, and oxidative stress markers like MDA, while enhancing antioxidant activity. It has been demonstrated that Cs supplementation can improve insulin sensitivity, reduce blood glucose levels, and enhance lipid metabolism in individuals with conditions such as diabetes and metabolic syndrome (MetS). These effects of Cs are believed to be mediated by its antioxidant characteristics, which aid in shielding cells from oxidative stress and inflammation. In general, Cs's antioxidant effect shows great potential in the treatment of metabolic disorders. Further research is warranted to elucidate the mechanisms of action and potential therapeutic applications of Cs in these conditions. The clinical effects of Cs on endocrine and metabolic disorders are summarized in Table 9.

Gastrointestinal and liver disorders

Each year, millions of individuals worldwide are impacted by gastrointestinal and liver disorders, posing a significant health concern. One potential treatment for these disorders is the use of antioxidants found in natural sources such as the Cs plant. Research has shown that Cs, which possesses antioxidant characteristics, can reduce oxidative stress in the gastrointestinal tract and liver. In a 12-week study, the effects of pure Cs supplementation in patients with NAFLD were investigated in a double-blind RTC; each patient received one tablet of Cs (100 mg/day). Results demonstrated that serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), TNF-α, body composition, and anthropometric indexes didn't change compared to placebo, but high-sensitivity C-reactive protein (hs-CRP), leptin, and MDA significantly decreased and TAC increased, indicating the effect of Cs on oxidative stress in patients with NAFLD (Kavianipour et al. 2020). A clinical trial investigated the effect of Cs (100 mg/day) on disease severity and oxidative/antioxidant factors in ulcerative colitis (UC) patients. The results indicate that Cs supplementation for 8 weeks significantly affects the severity of UC, the serum levels of TAC, SOD, and GPx, but MDA levels were not significantly changed. Therefore, Cs could be considered as an alternative therapy in improving antioxidant factors, which are key factors in UC development, and thus help to stop the progression of the disease (Tahvilian et al. 2021).

Cs supplementation has shown positive results in ameliorating gastrointestinal and liver disorders in clinical investigations. In patients with NAFLD, Cs significantly reduced hs-CRP, leptin, and MDA while increasing TAC. Similarly, in UC patients, Cs supplementation improved antioxidant factors, such as SOD and GPx, which reduce the severity of the disease. Furthermore, the antioxidant effect of Cs on the gastrointestinal tract and liver has been associated with its anti-inflammatory and anti-apoptotic properties. Chronic inflammation and cell death are common mechanisms underlying many gastrointestinal and liver diseases, such as IBD and NAFLD. Cs has been shown to inhibit inflammatory pathways and reduce apoptotic cell death, thereby protecting the gastrointestinal mucosa and liver tissue from damage. Overall, the gastrointestinal and liver antioxidant effect of Cs presents potential therapeutic benefits in preventing and managing various digestive and liver disorders. Therefore, the data suggest that Cs may serve as a potential adjunct therapy for gastrointestinal and liver conditions, though further high-quality trials are needed to confirm its efficacy. The clinical effects of Cs on gastrointestinal and liver disorders are summarized in Table 9.

Immunological and autoimmune disorders

The immunomodulatory effects, enhancing the body's immune response and providing protection against various diseases and infections of CS were indicated. In addition to its antioxidant and immunological benefits, Cs has also been studied for its potential role in autoimmune conditions. Studies have shown that the antioxidant effects of Cs may help to regulate the immune response and reduce inflammation in autoimmune disorders such as rheumatoid arthritis (RA). The effects of Cs supplements (100 mg/d) in patients with active RA led to a significant decrease in the number of tender and swollen joints, pain intensity, and disease activity score (DAS28) compared to the control group. Additionally, hs-CRP protein decreased in the Cs group compared to baseline values (Hamidi et al. 2020). The clinical effects of Cs on immunological and autoimmune disorders are summarized in Table 9.

Neurologic disorders

Complex nature and a wide variety of symptoms make neurologic disorders a challenging issue in the current-day medical practice. Among the potential therapeutics of these disorders, antioxidants have attracted the attention as neuro-protective agents. Cs is one of the hopeful antioxidants having rich potential causes in neurologic disorders. The plant has been used in traditional medicine to treat various disorders over centuries and is currently under research to find out whether it has neuro-protective properties. The treatment of Cs capsule (30 mg/day) during 12 weeks in group of donapesril in mild-to-moderate AD patients with 12 weeks decreased levels of IL-1b and MDA and improved the level of TAC in intervention group in a clinical trial. The outcomes indicated that Cs supplementation lacked any other effects on the cognitive outcomes, yet, it alleviated inflammatory and oxidative stress that possibly contributes to the beneficial impact of Cs supplementation on the circulation parameters in AD persons (Rasi Marzabadi et al. 2022). More research is required to clarify the mechanisms involved in the Cs effects on the brain and determining its optimum dosage and treatment time of supplementation. The potential of Cs as the natural means for treating neurologic disorders demonstrates the necessity in performing further studies in this field. The clinical effects of Cs on oxidative stress in neurologic disorders are summarized in Table 9.

Contraindications and potential drug interactions of *Crocus sativus*

Although Cs exhibits promising pharmacological properties and therapeutic potential, its clinical application is constrained by significant adverse effects and potential drug interactions that necessitate careful evaluation and monitoring. Cs is contraindicated in pregnancy due to its potential uterine stimulant effects, which could lead to miscarriage or premature labor. There is limited but concerning evidence regarding embryotoxicity at high dose (Butnariu et al. 2022).

Cs compounds can stimulate the contraction of the uterine muscles by interacting with smooth muscle receptors or influencing calcium channels, which enhances uterine contractility (Butnariu et al. 2022).

In higher amounts, Cs exhibits a spasmodic effect on the uterus, leading to risks of abortion and premature labor, as documented in both animal models and clinical observations (Butnariu et al. 2022). Experimental studies on mice have shown that administration of high doses of saffron during pregnancy resulted in increased uterine contractions and adverse pregnancy outcomes. On the other hand, high doses of Cs given to lactating mice, increased serum urea nitrogen and caused kidney tissue damage in their neonates, indicating potential nephrotoxicity, while no liver toxicity was observed. The study advises caution for nursing mothers regarding high saffron intake (Bahmani et al. 2014).

Cases of allergic reactions including itching, rash, and anaphylaxis have been reported rarely (Sut et al. 2024). Allergic reactions to saffron are primarily mediated by immunoglobulin E (IgE) antibodies that recognize saffron allergens. Upon allergen exposure, these IgE antibodies bind to mast cells and basophils, triggering their degranulation and release histamine and other mediators responsible for immediate hypersensitivity symptoms such as itching, rash, and in severe cases, anaphylaxis. Studies evaluating individuals exposed occupationally to saffron pollen found a sensitization rate and confirmed IgE-mediated responses, highlighting saffron as a relevant allergen in certain populations (Butnariu et al. 2022; Varasteh et al. 2007).

Caution is advised in patients with bleeding disorders or those on anticoagulant/antiplatelet therapy as saffron might potentiate bleeding risk via its blood-thinning or platelet aggregation inhibitory effects (Wani, Singh and Shukla 2022). CS contains bioactive compounds (e.g., crocin, safranal) shown in *in vitro* and *in vivo* studies to influence hemostasis by inhibiting platelet aggregation and coagulation factors such as factor Xa and cyclooxygenase-1 (COX-1). This can potentially increase bleeding risk, especially when combined with anticoagulant or antiplatelet drugs (Sinakosa and Geromichalosb 2016). Clinical trials investigating doses of Cs tablets (200-400 mg/day for one week) in volunteers showed no significant changes in coagulation parameters such as plasma fibrinogen, factor VII, protein C and S levels, prothrombin time (PT), or partial thromboplastin time (PTT). However, a mild increase in bleeding time was reported (Ayatollahi et al. 2014).

Cs mild hypotensive (blood pressure-lowering) effect could potentiate the action of antihypertensive drugs, leading to possible additive hypotension. The major active constituents responsible for the hypotensive effects are crocin and safranal (Imenshahidi et al. 2010). These compounds have shown dose-dependent reductions in mean arterial blood pressure (MABP) in normotensive and hypertensive animal models (Imenshahidi et al. 2010). Blocking of receptor-operated channels and calcium channels which are operated by voltage leads to relaxation by blocking intracellular calcium influx which is necessary in vascular smooth muscle contraction (Mokhtari-Zaer et al. 2015). Cs aqueous extract and crocin, 1, 10, and 200 mg/kg respectively, reduced the blood pressure by about 50, 51, and 60 mmHg, respectively, confirming the strong effect of hypotensive activity in rats (Imenshahidi et al. 2010).

Cs can have multiple drug interactions, mostly by inhibiting Cytochrome P450 enzymes including CYP3A4, CYP1A1/2 and CYP2E1. This process is capable of changing the metabolism of the drugs that are dependent on such enzymes, which may elevate blood levels and actions of drugs with a low therapeutic index, such as warfarin, cyclosporine and digoxin. Cs also regulates the immune action, and this may be disruptive to immunosuppressive drugs like cyclosporine or tacrolimus. Also, saffron can augment the possibility of bleeding among anticoagulants or antiplatelet drugs and augment the hypotensive impact of antihypertensive drugs (Bathaei et al. 2025).

Table 9. Antioxidant effects of *Crocus sativus* extracts and essential oil in the clinical studies

disorders	Clinical model	Dose, Duration	Effect	Ref.
Endocrine and metabolic	Prediabetes	100 mg/day 8 weeks	↓FBS, Glycosylated hemoglobin levels ↑Antioxidant activity	(Kermani et al. 2015)
		15 mg/day 8 weeks	↑DPPH radical scavenging activity ↓FBS, and HbA1c	(Karimi-Nazari et al. 2019)
	T2DM	100 mg/day 12 weeks	↓WC and MDA	(Ebrahimi et al. 2019)
		100 mg/day 8 weeks	↓NO, and MDA, FBS, lipid profile, atherogenic indices, and liver enzymes	(Tajaddini et al. 2023)
Gastrointestinal and liver	patients with NAFLD	100 mg/day 12 weeks	↑TAC ↓MDA, hs-CRP ↓Leptin	(Kavianipour et al. 2020)
	UC patients	100 mg/day 8 weeks	↑TAC, SOD, and GPx	(Tahvilian et al. 2021)
Immunological and autoimmune disorders	RA patients	100 mg/day 12 weeks	↑TAC ↓hs-CRP	(Hamidi et al. 2020)
Neurologic	AD patients	30 mg/day 12 weeks	↓ MDA ↑TAC	(Rasi Marzabadi et al. 2022)

Abbreviations: Ref: references, T2DM: type 2 diabetes mellitus, FBS: fasting blood sugar, DPPH: α, α-diphenyl-β-picrylhydrazyl, HbA1c: Hemoglobin A1C, WC: Waist circumference, MDA: Malondialdehyde, NO: nitric oxide, TAC: total antioxidant capacity, GPx: Glutathione peroxidase, NAFLD: nonalcoholic fatty liver disease, SOD: superoxide dismutase, hs-CRP: hs-CRP: High-sensitivity C-reactive, AD: Alzheimer disease, AR:Rheumatoid arthritis, UC: Ulcerative colitis.

Discussion

Cs is an effective medicinal herb that shows positive results in modulating a wide range of diseases. It medicinal effects attributes to free radical scavengers and it possesses greater health advantages over their synthetic counterparts. Cs is rich in phytochemicals like crocin, crocetin, safranal, and picrocrocin, which are attributed to its significant biological properties. These are very potent anti-oxidant, anti-inflammatory neuroprotective & anticancer in nature.

Cs expresses protective action against cardiovascular disease by lowering cholesterol level, blood pressure and improving blood vessel functions. Studies have indicated that crocetin, one bioactive component in Cs, has the capacity to inhibit oxidative stress and inflammation in the cardiovascular system. The anti-inflammatory properties of Cs may help prevent atherosclerosis, a condition in which plaque clogs the arteries, increasing the risk of heart attack and stroke.

Clinical investigations on the effects of Cs and its constituents have shown, the improvement of various health related disorders especially metabolic disorders through their antioxidant property. It was demonstrated that Cs reduced markers of oxidative stress in people with higher risk of cardiovascular disease and T2DM in patients with MetS. A Supplement consumption of Cs extracts could improve the amount of antioxidant and improve the lipid profile of patients with coronary artery disease. These results indicate that Cs and its bioactive compounds are valuable supplementation in treatment and prevention of oxidative-related chronic diseases.

Different studies have shown that Cs potentially have cancer protection capacity, by its effects on proliferation of cancer cells and triggers apoptosis. The carotenoid compound of Cs known as crocin also showed anti-cancer properties due to its ability to reduce inflammation and oxidative stress as well as reduce growth of cancer cells. Moreover, Cs has been proved to optimize the use of chemotherapy and radiotherapy for treating cancer. The antioxidant properties of the plant protect against DNA damages and mutations that may contribute to growth of cancer. The potential preventive effects of Cs and its constituent on neurodegenerative diseases like AD and PD has been attributed to its antioxidant properties. The plant and its constituent can affect neuronal damages and cognitive decline by their effects on oxidative stress. The outcomes of the published articles show that the antioxidant properties of Cs and its constituents may play a significant role in preventing the oxidative stress of neurons and the inflammation of the brain. Some experimental and clinical works also showed that Cs and its derivatives are helpful in the treatment of gastrointestinal disorders, as well as immunological, respiratory, and urogenital disorders through their antioxidant properties. Various antioxidant mechanism of Cs and its constituents are shown Figures 3 and 4.

In general, the antioxidant characteristics of Cs have important implications for human health. Since oxidative stress is linked to the onset of many diseases. Adding Cs to the diet or taking it as a supplement can aid in preventing cell damage and improving overall well-being. More studies are required to fully grasp how Cs works as an antioxidant and to establish the more effective dosage and duration for different health issues. Nevertheless, current evidence indicates that Cs and its derivatives could be a beneficial treatment for fighting oxidative stress and enhancing longevity. In summary, Cs and its components provide a valuable natural treatment for preventing various illnesses. Improving overall health and reducing the risk of chronic diseases, such as cardiovascular, neurodegenerative, gastrointestinal, neuronal, respiratory, and urogenital disorders as well as cancer, could be achieved through its ability to neutralize free radicals, reduce inflammation, and protect cells from oxidative damage. More studies are needed to better understand how with Cs antioxidant characteristics effects on various disorders and to determine the most effective doses and methods of administration for medicinal use.

Finally, Cs exhibits various pharmacological benefits; however, its clinical use is limited by contraindications and drug interactions. Notably, saffron may potentiate the effects of anticoagulant and antiplatelet agents, increasing bleeding risk, and can interact with antihypertensive drugs leading to additive hypotensive effects. Additionally, Cs inhibitory action on cytochrome P450 enzymes (especially CYP3A4) raises concerns about altered metabolism and toxicity of co-administered drugs such as warfarin and cyclosporine. Therefore, careful consideration and monitoring are required when saffron is used concomitantly with other medications, particularly in vulnerable populations such as pregnant women and those with bleeding disorders.

Numerous studies of the therapeutic value of Cs are based on small samples, short-term studies, and non-standardization of extracts or dose. The approach of methodology, biological models, and inclusion criteria are strongly heterogeneous, which leads to the problem of creating consistent conclusions and comparing the results of the study. Moreover, the geographical scope of most clinical research is restricted to specific areas and this could impact on the generalizability to the larger populations. The results of preclinical animal models experiments may not always be directly applicable to human outcomes due to the differences between animal physiology and disease complexity compared to humans, plus such factors as age, genetic variation, and comorbidities.

Cs clinical trials and observational studies on Cs show mixed results on efficacy. Even though certain studies have shown positive effects in such domains as inflammation, mood control, and even particular metabolic or autoimmune disorders, others have found minimal or statistically no significant ones. The discrepancies highlight that to characterize therapeutic effects and substantiate results, it is needed to conduct large-scale and multicentered randomized controlled trials.

The review shows that Cs is a promising source of antioxidants and various phytochemicals and holds significant experimental and initial clinical outcomes. Nevertheless, differences in study outcomes, approach shortcomings, and unsolved safety concerns are reasons to be cautious and approach the matter of the large-scale application of saffron extracts through a more systematic study.

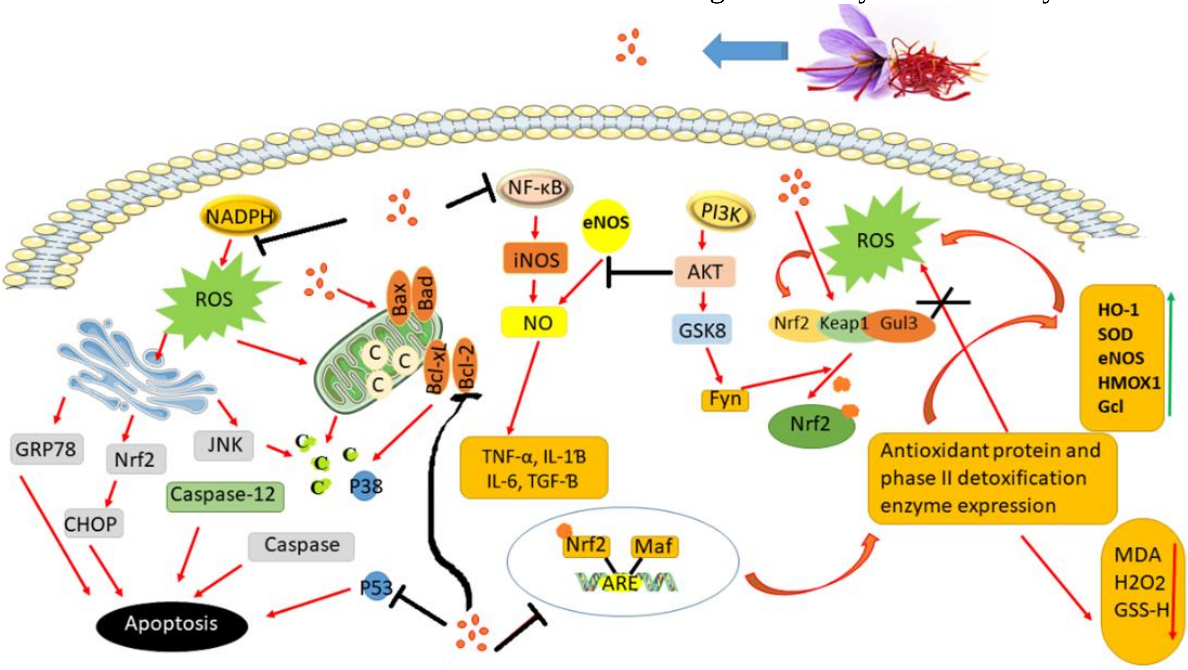

Figure 3. Antioxidant mechanism of *Crocus sativus* and its constituents

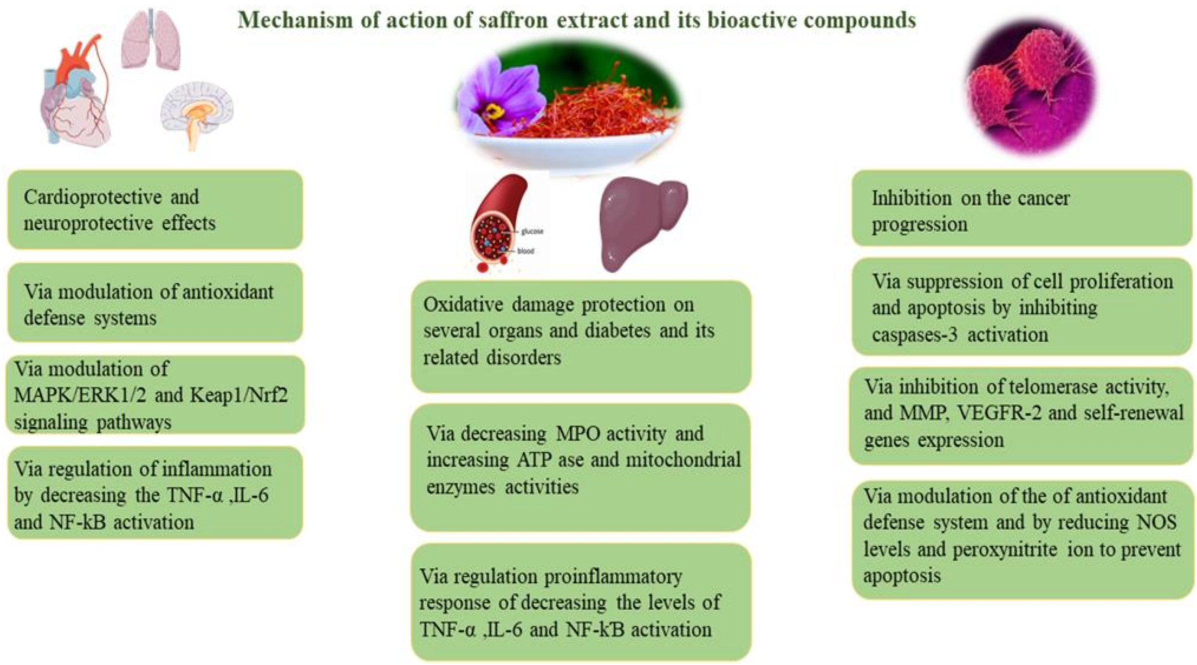

Figure 4. Possible mechanisms of antioxidant effects of *Crocus sativus* in the different organs

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Conflicts of interest

The authors declare that they have no competing interests.

CRediT author statement

FZ: Writing original draft. SB: Writing, review & editing. MHEGH: Writing review & editing. MSB: Writing, review & editing. SMS: Writing, review & editing. MHB: Writing, original draft, methodology, and funding acquisition. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

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