IJTMGH International Journal of Travel Medicine and Global Health

Int J Travel Med Glob Health. 2026 Mar;14(1):1-12
http://ijtmgh.com

doi 10.30491/ijtmgh.2025.501673.1454

Review Article Open Access

The Therapeutic Promise of Crocin: From Neuroprotection to Anticancer Effects

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Received 2025-01-23; **Accepted** 2025-03-17; **Online Published** 2026-03-01

Abstract

Crocin, a bioactive compound derived from saffron (Crocus sativus), has garnered significant attention in recent research due to its wide-ranging pharmacological properties, particularly in the realms of neuroprotection, anti-inflammatory responses, and cancer treatment. This compound shows promise in treating neurodegenerative diseases such as Alzheimer's and Parkinson's by reducing beta-amyloid aggregation and increasing dopamine levels. Additionally, crocin exhibits strong anti-inflammatory and antioxidant activities, acting as a radical scavenger that safeguards various tissues, including the brain, heart, and kidneys, while also inhibiting acetylcholinesterase activation. Its cardioprotective effects are evident through improvements in cardiovascular health, evidenced by reductions in blood pressure and enhanced endothelial function, as well as protection against ischemia/reperfusion injury. Furthermore, crocin has demonstrated anticancer effects, showing cytotoxicity against various cancer cell lines, inhibiting tumor growth, and enhancing survival rates in animal models without significant toxicity. Beyond these effects, crocin may also help manage metabolic disorders like diabetes and obesity by modulating lipid profiles and improving energy metabolism, along with exhibiting antidepressant properties and enhancing memory function. Clinical trials indicate that crocin is generally safe for consumption at therapeutic doses, with no significant adverse effects noted at 20 mg/day, supporting its potential as a functional food ingredient or dietary supplement. Overall, crocin's diverse pharmacological effects make it a promising candidate for various therapeutic applications, and ongoing research continues to explore its mechanisms of action and potential benefits, particularly in neuroprotection and cancer treatment, suggesting that it may play a crucial role in managing chronic diseases and improving overall health outcomes.

Keywords: Crocin, Neuroprotection, Anti-inflammatory, Antioxidant activities, Anticancer effects, Metabolic disorders.

Citation: Ahsani A, Saberi M, Mashhadhi Akbar Boojar M. The Therapeutic Promise of Crocin: From Neuroprotection to Anticancer Effects. Int J Travel Med Glob Health, 2026;14(1):1-12. Doi: 10.30491/ijtmgh.2025.501673.1454.

Introduction

Saffron, derived from the stigma of Crocus sativus L., has a rich history in medicine dating back to ancient civilizations. Its therapeutic applications have been recognized across various cultures, with significant attention to its active compounds, particularly crocin [1]. Historically, saffron was utilized in ancient medicine for its antispasmodic, expectorant, and antidepressant properties [2-4]. It served dual roles as a spice and a remedy for ailments ranging from respiratory issues to mental health disorders. During the European Renaissance, saffron was included in plague remedies and was noted for its restorative effects on the brain and heart [4]. In modern applications, phytochemical research has identified crocin as a key bioactive compound with antioxidant, anti-inflammatory, and neuroprotective effects [5,6]. Clinical trials have shown that saffron extracts are promising in treating cognitive decline, particularly in Alzheimer's patients, underscoring its potential in contemporary therapies [7]. While the historical significance of saffron is well documented, contemporary research continues to explore its full medicinal potential, indicating a renewed interest in its applications in modern medicine.

Crocin, a prominent carotenoid in saffron, exhibits significant physicochemical properties that enhance its health benefits. It is renowned for its high antioxidant capacity, with an inhibitory concentration 50% (IC50) value of 283.918 μg/mL, and demonstrates notable antimicrobial activity, particularly against Staphylococcus epidermidis, with an inhibition zone of 6.0 mm at 100 μg/mL [8]. Iranian saffron boasts the highest crocin concentration (11,414.67 μg/g DW) compared to other regions [8,9]. Compared to other saffron components, such as picrocrocin, which contributes to its flavor, and safranal, which enhances its aroma [10], crocin stands out for its anti-cancer and anti-inflammatory properties. However, the sensory attributes provided by picrocrocin and safranal are equally crucial for saffron's culinary and medicinal applications, underscoring the multifaceted nature of this spice [11].

The hypothesis of this study posits that crocin, a key bioactive compound derived from saffron, exerts a wide range of pharmacological effects that can significantly contribute to various health benefits. The objective is to provide a comprehensive and up-to-date review of the existing literature on the pharmacological properties of crocin, focusing on its antioxidant, anti-inflammatory, anticancer, and neuroprotective effects. By synthesizing recent findings, this study aims to elucidate the mechanisms underlying these effects and to highlight the therapeutic potential of crocin in contemporary medicine, thereby fostering further research and clinical applications.

Methods

In the current narrative review study, the electronic databases including Web of Sciences, Scopus, and Pubmed were comprehensively searched for the pharmacological effects of crocin for articles published from 2000 to the end of 2024, using the keywords "Crocin, Neuroprotection, Anti-inflammatory, Antioxidant activities, Anticancer effects, Metabolic disorders" in the title, abstract, and keywords. References from retrieved articles were also manually reviewed.

Results

Crocin, a key bioactive compound derived from saffron, exhibits a wide range of pharmacological properties that have garnered significant attention in recent research. Its therapeutic applications span various health conditions, particularly in neuroprotection, anti-inflammatory responses, and cancer treatment (Fig. 1). Also, a summary of major related investigations including cell culture, animal, and clinical studies is presented in Table 1.

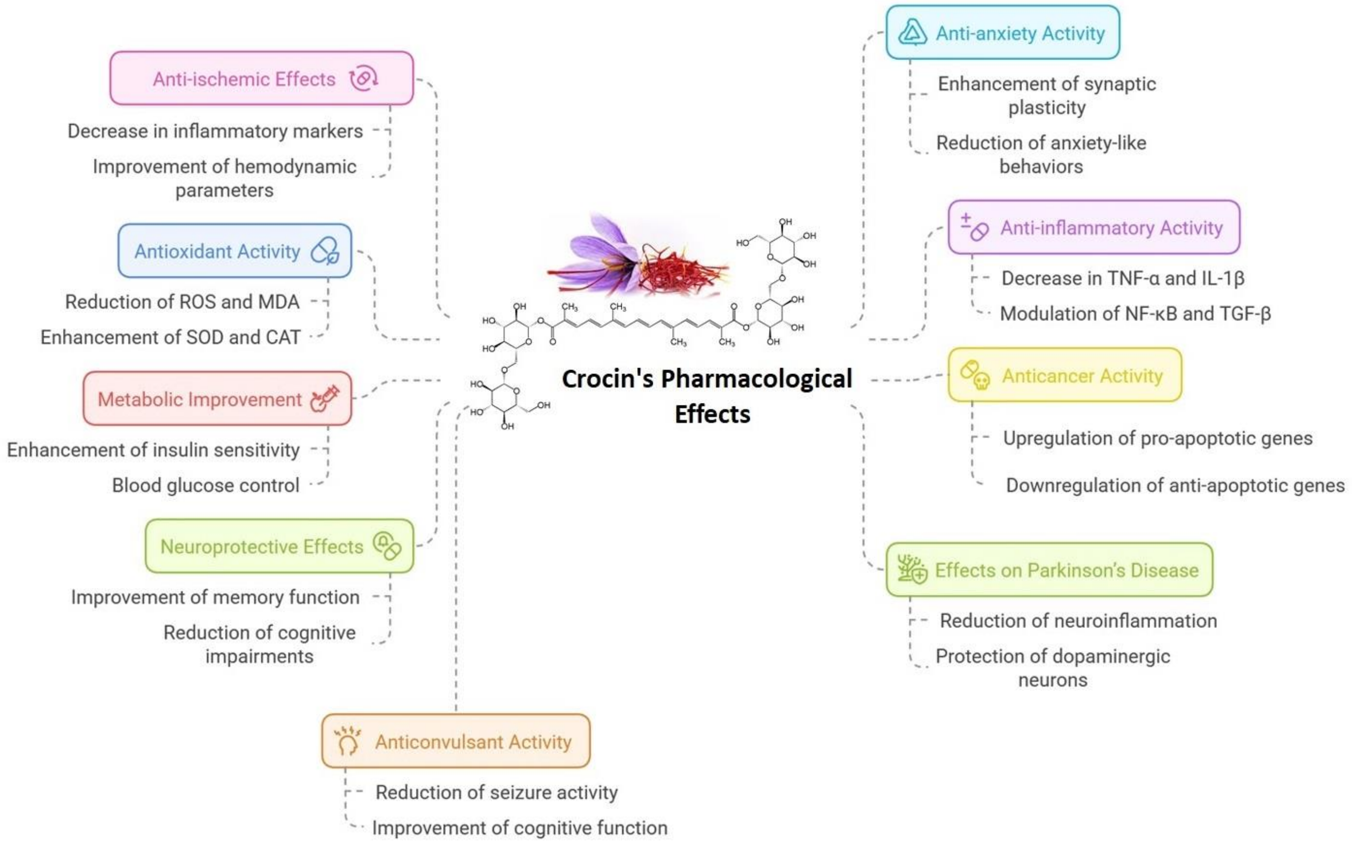

Fig. 1. The Pharmacological effects of crocin at a glance.

The cytotoxic effects

The cytotoxic effects of crocin, have been extensively studied in various laboratory models, demonstrating its potential as an anticancer agent. Research indicates that crocin exhibits significant cytotoxicity against different cancer cell lines, often enhanced when formulated as nanoparticles or liposomes. For instance, crocin nanoparticles (Cro-NPs) showed higher cytotoxic effects against HepG2 cells (IC50 = 1.1 mg/mL) compared to native crocin (IC50 = 6.1 mg/mL) [12]. In MDA-MB-231 breast cancer cells, crocin increased the cytotoxicity of doxorubicin, with liposomal formulations further amplifying this effect [13]. Additionally, crocin and nanocrocin reduced zearalenone-induced cytotoxicity in HEK293 cells, improving cell survival and antioxidant enzyme activity [14]. Mechanistically, crocin treatments induced apoptosis in cancer cells, evidenced by the upregulation of pro-apoptotic genes j and downregulation of anti-apoptotic genes (B-cell lymphoma 2 (BCL-2)) [13,15]. Flow cytometry analysis revealed that crocin treatment caused cell cycle arrest in the G2/M phase, contributing to its cytotoxic effects [13]. Furthermore, using nanoparticles and liposomes significantly improved the stability and bioavailability of crocin, leading to enhanced cytotoxic effects compared to conventional formulations[16].

Crocin shows significant cytotoxic effects against various cancers, particularly breast cancer, as evidenced by multiple studies. Specifically, crocin has been shown to induce apoptosis in breast cancer cells by activating procaspase-9 and increasing stress response markers, leading to cell death [17]. Additionally, it downregulates the tumor-promoting microRNA miR-122-5p while upregulating tumor suppressors such as forkhead box P2 (FOXP2) and sprouty protein 2 (SPRY2), effectively inhibiting cancer cell proliferation [18]. In vivo studies in mice models have demonstrated that crocin reduces tumor volume and improves survival rates by downregulating pro-metastatic factors such as vascular endothelial growth factor (VEGF) and matrix metalloproteinase 9 (MMP9). Furthermore, its low toxicity suggests potential as a complementary treatment in clinical settings, particularly when combined with standard therapies [19].

Metabolic effects

The metabolic effects of crocin, have been extensively studied in both animal models and clinical settings, highlighting its potential in managing various metabolic disorders. Research indicates that crocin possesses significant hypoglycemic, anti-inflammatory, and antioxidant properties, contributing to improved metabolic health [20]. Notably, crocin has shown promising results in enhancing glycemic control among patients with metabolic syndrome, potentially reducing the risk of cardiovascular diseases [21]. In animal studies, crocin administration improved insulin sensitivity and lowered blood glucose levels, underscoring its role in diabetes management [22]. Furthermore, crocin mitigates diabetic nephropathy by regulating metabolic pathways and reducing oxidative stress, which is crucial for kidney health [23]. In non-alcoholic steatohepatitis (NASH) models, crocin demonstrated hepatoprotective effects by decreasing inflammation and apoptosis through the Fas signaling pathway [24]. Additionally, crocin prevented weight gain and insulin resistance in ovariectomized mice, indicating its potential in addressing metabolic dysfunction in postmenopausal women [25].

Memory improvement effects

Saffron demonstrates antioxidant properties across various neurological disorders, including neurodegenerative and psychological conditions. Some of these pharmacological benefits are attributed to its crocin content [26]. The effects of crocin on memory have been extensively studied in both animal models and clinical environments, demonstrating its potential as a neuroprotective agent. Research indicates that crocin can alleviate cognitive impairments caused by various stressors and neurotoxic factors, enhancing memory function and synaptic plasticity [27]. In animal studies, the administration of crocin has shown significant improvements in spatial memory tasks, such as the Morris water maze, particularly in models of cognitive impairment induced by stress [28]. Mechanistically, crocin enhances long-term potentiation (LTP) in hippocampal neurons, which is crucial for memory formation, while also reducing anxiety-like behaviors [29]. It also inhibits acetylcholinesterase activation [6]. Furthermore, in oxidative damage models, crocin has been effective in restoring normal antioxidant levels and reducing markers of neuroinflammation, thereby improving cognitive performance [30]. Clinically, crocin has been proposed as a potential adjunct therapy for cognitive deficits associated with psychiatric disorders, such as schizophrenia, by addressing memory impairments resulting from N-methyl-D-aspartate (NMDA) receptor antagonism [31].

Anti-parkinson's disease effects

Crocin has revealed promising effects in experimental research related to Parkinson's disease (PD). Its neuroprotective properties are linked to its ability to reduce neuroinflammation, enhance the survival of dopaminergic neurons, and alleviate related depressive symptoms [32]. For instance, crocin significantly increases the expression of tyrosine hydroxylase, a marker for dopaminergic neurons, in LPS-induced PD models [33]. In MPTP-induced models, crocin treatment improved motor deficits and protected dopaminergic neurons from damage [34]. Additionally, crocin reduces levels of inflammatory cytokines like Interleukin-1 beta and caspase-1, which are elevated in PD models [33]. It also decreases the expression of genes associated with neuroinflammation, such as NOD-like receptor protein 1 (NLRP1) and absent in melanoma 2 (AIM2) [33]. Furthermore, in PD models exhibiting depressive-like behavior, crocin treatment improved symptoms by enhancing synaptic plasticity through mammalian target of rapamycin (mTOR) signaling pathways [35].

Anti- ischemia effects

Crocin protective mechanisms primarily involve the reduction of inflammation, enhancement of antioxidant activity, and improvement of hemodynamic parameters. In animal models, crocin significantly decreased inflammatory markers (tumor necrosis factor-alpha (TNF-α), interleukin-6, interleukin-1 beta) and improved antioxidant enzyme levels (superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX)) in the gastrocnemius muscle subjected to ischemia-reperfusion injury [36]. Furthermore, in myocardial infarction models, crocin administration reduced apoptosis and inflammatory cytokine levels, indicating its role in protecting cardiac tissue against ischemic damage [37]. Mechanistically, crocin enhances antioxidant enzyme activities and mitigates oxidative stress induced by ischemia [38]. Additionally, it modulates key inflammatory pathways, including kelch repeat and BTB domain containing 7 (KBTBD7)-mediated signaling, which is crucial for reducing excessive inflammation following myocardial infarction[37]. Clinically, crocin has been associated with neuroprotective effects in ischemic stroke, although further clinical validation is necessary [39].

Anti-oxidative and anti-inflammatory effects

Crocin acts as a direct scavenger of free radicals, significantly reducing oxidative stress markers such as reactive oxygen species (ROS) and malondialdehyde (MDA) in human umbilical vein endothelial cells (HUVECs) and intestinal epithelial cells (IPEC-J2) [40,41]. Additionally, it enhances the activity of antioxidant enzymes, including SOD and CAT, thereby stabilizing cellular redox homeostasis [42,43]. On the anti-inflammatory front, crocin significantly reduces the expression of pro-inflammatory cytokines such as TNF-α and interleukin-1 beta, contributing to its anti-inflammatory properties. Moreover, it modulates key signaling pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and transforming growth factor-beta (TGF-β), which play critical roles in inflammatory responses [44].

Crocin also has demonstrated efficacy in reducing inflammatory biomarkers and improving clinical outcomes in patients with conditions such as multiple sclerosis, inflammatory bowel disease, ulcerative colitis, thyroid eye disease, and chronic obstructive pulmonary disease [45]. On the anti-inflammatory front, a clinical trial revealed that crocin supplementation significantly reduced inflammatory biomarkers (high-sensitivity C-reactive protein (hs-CRP)) in patients with multiple sclerosis, demonstrating its potential to mitigate inflammation in chronic conditions [46]. Similarly, high doses of saffron-containing crocin led to a notable reduction in inflammatory markers like fecal calprotectin and CRP in patients with ulcerative colitis. Clinically, crocin supplementation has been associated with improved clinical scores in ulcerative colitis and chronic obstructive pulmonary disease, enhancing patients' quality of life and exercise capacity [47,48]. In thyroid eye disease, crocin contributed to reduced clinical activity scores and inflammatory cytokines, although no significant differences were observed between treatment groups [49].

Neuroprotective effects

Research shows that crocin effectively reduces oxidative stress, inflammation, and apoptosis, thereby maintaining neuronal integrity and function. Its neuroprotective mechanisms include lowering MDA levels and enhancing antioxidant enzyme activity in models of nicotine-induced neurodegeneration[50], decreasing pro-inflammatory cytokines associated with neurodegenerative conditions[43], and modulating apoptotic pathways to reduce neuronal cell death. Additionally, crocin has demonstrated beneficial effects in various neurological disorders, including improving behavioral outcomes and reducing neuroinflammation in nicotine-treated mice [50], offering protection against cerebellar damage from electromagnetic field exposure [51], and showing promise in reducing seizures and behavioral deficits in epilepsy models and reversing oxidative damage in autism induced by valproate [52,53].

Anti-anxiety effects

Crocin exhibits tranquilizer properties and modulates neurotransmitter systems, positioning it as a potential alternative to conventional anxiolytics. Evidence supporting its efficacy in reducing anxiety includes a study with nursing students, which found that saffron containing crocin significantly lowered anxiety levels from 13.8 to 9.2 after two weeks of treatment [54].

Additionally, a meta-analysis comparing saffron with serotonin reuptake inhibitors (SSRIs) indicated a significant difference in anxiety reduction, suggesting saffron as a viable alternative with fewer side effects [55]. Mechanistically, crocin enhances synaptic plasticity and reduces anxiety-like behaviors in animal models through the activation of the phosphoinositide 3-kinase (PI3K)/ protein kinase B (Akt)/mTOR signaling pathway [56,57] and functions as a monoamine oxidase inhibitor, potentially increasing neurotransmitter levels such as serotonin, thereby contributing to its anxiolytic effects [58].

Anticonvulsant effects

Research indicates that crocin can effectively reduce seizure activity and enhance cognitive functions in animal models of epilepsy and neurotoxicity. It has been shown to inhibit neuroinflammation and oxidative stress in epilepsy models, thereby increasing neuronal survival and cognitive performance [52]. Additionally, in studies on methamphetamine neurotoxicity, crocin treatment significantly elevated antioxidant levels and reduced markers of apoptosis and inflammation in the hippocampus [59]. In a rapid-onset epilepsy model, crocin administration led to a decrease in the incidence of generalized seizures and slowed the progression of seizure stages [60]. Furthermore, its ability to modulate α2-adrenergic receptors in the anterior cingulate cortex suggests a role in pain and anxiety management, which may indirectly affect seizure thresholds [61]. Crocin has also shown promise in improving memory and mitigating learning deficits associated with neurodegenerative conditions, indicating broader therapeutic implications beyond seizure control [30].

Effects on respiratory tract

Research indicates that crocin can alleviate conditions such as acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), and eosinophilic nasal polyps by modulating inflammatory pathways and enhancing lung function. It reduces inflammatory cytokines like TNF-α, interleukin-6, and interleukin-8 in response to stimuli such as lipopolysaccharides and Aspergillus fumigatus, thereby decreasing airway inflammation [62]. Additionally, crocin inhibits the NF-κB signaling pathway, a crucial mediator of inflammation activated in various respiratory conditions [63,64]. In COPD patients, crocin supplementation has been shown to improve exercise capacity and create a better oxidant/antioxidant balance, evidenced by enhanced pulmonary function tests and reduced total oxidant status [65]. It also protects against glycocalyx damage in ARDS and aids in improving pulmonary vascular permeability [66]. The mechanisms of crocin's action include its ability to suppress oxidative stress and inflammatory signaling pathways, including the inhibition of matrix metalloproteinases and heparanase [64], and it has been shown to relax airway smooth muscle, further supporting respiratory function [67].

Renal protective effects

Crocin, exhibits remarkable renal protective effects through various mechanisms, particularly in conditions such as diabetic nephropathy and drug-induced nephrotoxicity. Research shows that crocin enhances autophagy, reduces oxidative stress, and modulates inflammatory pathways, thereby contributing to its therapeutic potential for kidney health. It inhibits epithelial-mesenchymal transition (EMT) in renal tubular cells by activating the adenosine monophosphate - activated protein kinase (AMPK)/mTOR pathway and promoting autophagy [68]. Additionally, in models of doxorubicin-induced nephrotoxicity, crocin increases the activity of antioxidant enzymes (SOD, CAT) and decreases oxidative stress markers, protecting renal architecture [42]. Furthermore, crocin reduces pro-inflammatory markers (interleukin-1β, TGF-β) and apoptosis-related genes while upregulating protective factors like nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1), underscoring its role in mitigating inflammation and apoptosis in gentamicin-induced nephrotoxicity [69,70]. Its ability to lower TGF-β levels and improve glyoxalase activity suggests crocin's potential in managing diabetic nephropathy, while the activation of the Sirtuin 1 (siRT1)/Nrf2/HO-1 pathway highlights its promise in treating membranous nephropathy by reducing immune damage and podocyte injury [71].

Cardiovascular protective effects

Crocetin demonstrates significant cardioprotective effects through various mechanisms, showing that it reduces oxidative stress, inflammation, and dyslipidemia, thereby contributing to improved heart health. The antioxidant properties of crocetin act as a direct scavenger of free radicals, reducing oxidative stress in cardiac cells [40]. Furthermore, it enhances the activity of myocardial antioxidant enzymes, leading to decreased levels of MDA and ROS in heart failure models [72]. The anti-inflammatory effects of crocetin include modulation of inflammatory pathways, particularly the inhibition of the Toll-like receptor 4 (TLR4)/NF-κB signaling pathway, which is crucial in cardiac inflammation, significantly reducing inflammatory cytokines such as interleukin-1β, interleukin-6, and TNFα, thus protecting myocardial tissue from damage [37]. Additionally, crocetin has been shown to normalize lipid profiles and potentially prevent cardiovascular complications associated with dyslipidemia, influencing intracellular pathways that regulate fat metabolism and providing a safer alternative to pharmacological interventions [73].

Effects on the gastrointestinal system

Research demonstrates that crocin can effectively reduce oxidative stress, inflammation, and dysbiosis, enhancing gut health and preventing gastrointestinal disorders. It decreases oxidative stress markers such as ROS and MDA while increasing the activity of antioxidant enzymes like SOD and CAT in intestinal cells [41]. Moreover, crocin modulates the NF-κB signaling pathway to suppress inflammation, leading to decreased levels of pro-inflammatory cytokines in conditions such as ulcerative colitis and colorectal cancer [74]. Additionally, crocin-I alters gut microbiota composition by reducing harmful bacteria and increasing beneficial short-chain fatty acids (SCFAs) in dietary-induced obesity models [75]. It also restores microbiota diversity disrupted by chronic glucocorticoid treatment, indicating its potential in managing gut dysbiosis [76]. Finally, in models of nonsteroidal anti-inflammatory drugs (NSAIDs)-induced intestinal ulcers, crocin shows significant protective effects by reducing inflammation and apoptosis, thus maintaining intestinal integrity [77].

Dermatologic effects

Crocin demonstrates considerable dermatological effects, particularly concerning skin cancer and inflammatory skin conditions. Research indicates that crocin can inhibit pathways associated with inflammation and fibrosis, making it a promising therapeutic agent for various skin disorders. Specifically, it reduces tumor formation in chemical-induced skin cancer models by inhibiting the Wnt/β-catenin pathway, which is critical for cancer progression, and promotes apoptosis in human skin cancer cells by downregulating the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway, leading to decreased cell survival and proliferation [78]. In models of atopic dermatitis, crocin significantly lowers dermatitis scores, ear thickness, and inflammatory markers such as TNF-α and interleukin-1β, while also diminishing the Th2 immune response, thereby alleviating inflammation associated with skin conditions [79]. Furthermore, crocin protects skin fibroblasts from ultraviolet B radiation (280 to 320 nanometers)-induced damage by reducing ROS and enhancing the expression of antioxidant proteins and collagen, which are essential for skin integrity [80].

The role of crocin in mitigating chemotherapy-related side effects

Crocin has been studied for its potential therapeutic effects, particularly in mitigating chemotherapy-related side effects. While crocin exhibits protective properties against various forms of toxicity, it is essential to recognize the potential side effects associated with its use. For instance, crocin has demonstrated nephroprotective effects against nephrotoxicity induced by doxorubicin, improving kidney function and reducing oxidative stress markers [81]. However, some studies have reported that the administration of crocin during chemotherapy is associated with increased instances of leukopenia and hypersensitivity reactions compared to placebo groups [82]. Additionally, animal studies indicate that crocin ameliorates the adverse effects of cyclophosphamide on ovarian tissue, suggesting a protective role against reproductive toxicity [83]. Despite these benefits, the long-term impact of crocin on reproductive health remains to be thoroughly investigated.

Table 1. Pharmacological effects of crocin: a review of cell culture, animal, and clinical studies.

Type	Study Design	Cell/Animal Source	Findings	Reference
Cell Culture Study	Crocin nanoparticles (Cro-NPs) vs. native crocin	human liver cancer	Cro-NPs showed higher cytotoxicity against HepG2 cells (IC50 = 1.1 mg/mL) compared to native crocin (IC50 = 6.1 mg/mL).	(12)
Cell Culture Study	Crocin with doxorubicin on MDA-MB-231 cells	human breast cancer	Crocin increased the cytotoxicity of doxorubicin; liposomal formulations further amplified this effect.	(13)
Cell Culture Study	Zearalenone-induced toxicity in HEK293 cells	human embryonic kidney	Crocin and nanocrocin improved cell survival and antioxidant enzyme activity.	(14)
Animal Study	In vivo cancer model	Mice	Crocin reduced tumor volume and improved survival rates by downregulating pro-metastatic factors.	(19)
Animal Study	Crocin in diabetic nephropathy models	Rats	Mitigated diabetic nephropathy through regulation of metabolic pathways and reduction of oxidative stress.	(23)

Type	Study Design	Cell/Animal Source	Findings	Reference
Animal Study	Crocin on NASH models	Mice	Demonstrated hepatoprotective effects by decreasing inflammation and apoptosis.	(24)
Animal Study	Crocin in ovariectomized mice	Mice	Prevented weight gain and insulin resistance, indicating potential for postmenopausal metabolic dysfunction.	(25)
Animal Study	Crocin in PD models	Mice	Enhanced survival of dopaminergic neurons and improved motor deficits.	(34)
Animal Study	Crocin on ischemic models	Rats	Reduced inflammatory markers and improved antioxidant enzyme levels in ischemia-reperfusion injury.	(36)
Animal Study	Crocin in respiratory distress models	Mice	Reduced airway inflammation and improved lung function.	(62)
Animal Study	Crocin in renal protection studies	Rats	Enhanced autophagy and reduced oxidative stress in renal tubular cells.	(68)
Clinical Trial	Crocin in multiple sclerosis patients	N/A	Significantly reduced inflammatory biomarkers (hs-CRP).	(46)
Clinical Trial	Crocin in ulcerative colitis	N/A	Notable reduction in inflammatory markers and improved clinical scores.	(47)
Clinical Trial	Crocin for COPD patients	N/A	Improved exercise capacity and pulmonary function tests.	(48)
Clinical Trial	Crocin supplementation in patients with diabetes	N/A	Improved oxidative stress and renal function parameters.	(20)
Clinical Trial	Crocin for metabolic syndrome patients	N/A	Enhanced glycemic control and cardiovascular risk reduction.	(21)

Possible adverse effects of crocin

While crocin offers numerous health benefits, its safety profile is not entirely devoid of concern. Potential side effects include cardiovascular impacts, as excessive doses may alter hemodynamic parameters and exacerbate cardiac conditions in sensitive individuals [38,84]. Additionally, while crocin has shown neuroprotective effects against substances like nicotine, the long-term effects of high doses on cognitive functions remain unknown [43]. Furthermore, despite its antioxidant properties, interactions with other oxidative stressors, such as paraquat, may lead to complex responses that could negate its benefits if not managed properly [85]. Clinical trials have indicated that crocin is generally safe for consumption at therapeutic doses. For instance, a study involving healthy volunteers found no significant adverse effects when administered at a dosage of 20 mg/day

Possible food and drug interaction of crocin

Crocin may interact with various foods and medications, potentially impacting its therapeutic effects and safety. For instance, grapefruit juice can inhibit cytochrome P450 enzymes, affecting crocin metabolism and altering its efficacy [86]. Additionally, high-fat meals may enhance crocin absorption, leading to increased bioavailability [87].

Regarding drug interactions, crocin may potentiate the effects of anticoagulants and antiplatelet drugs, increasing the risk of bleeding [88]. It could also influence serotonin levels, posing a risk when combined with SSRIs, and may lower blood sugar levels, enhancing the effects of antidiabetic medications [89,90]. Given these potential interactions, it is crucial to consult a healthcare provider before using crocin, especially for individuals on medication or with underlying health conditions.

Novel pharmaceutical dosage form of crocin

While crocin shows promising pharmacologic effects in laboratory conditions, its clinical application may be limited by factors such as bioavailability and stability. It has been explored in various new pharmaceutical forms to enhance its therapeutic efficacy and bioavailability. Recent studies focus on innovative delivery systems, including soft chewable dosage forms and nanostructured lipid dispersions, aimed at improving the stability and release profile of crocin [91]. The newly developed soft chewable forms encapsulate crocin in lipid materials, enhancing gastrointestinal absorption and patient compliance [92]. Additionally, research on nanostructured lipid dispersions has demonstrated their effectiveness for topical administration of crocin, increasing its antioxidant and antiproliferative properties [93]. These dispersions protect crocin from degradation, control its release in the skin, and prolong its antioxidant activity, making it suitable for treating skin-related conditions. However, challenges remain in optimizing these formulations for various clinical applications, particularly in ensuring consistent release profiles and patient acceptance.

Comparison of the pharmacological effects of crocin and safranal

Crocin and safranal, two active compounds extracted from saffron, each have unique yet complementary pharmacological properties that can be used as effective therapeutic agents in various conditions. Crocin is particularly known for its antioxidant, anti-inflammatory, and anticancer properties, and studies have shown that this compound can help induce apoptosis in cancer cells and improve blood sugar metabolism. In particular, crocin exhibits potent anticancer properties by inducing apoptosis in cancer cells and inhibiting tumor invasion, especially in prostate and lung cancers, and enhances the effectiveness of conventional chemotherapy drugs [94,95]. In contrast, safranal is mainly known as a sedative, anti-anxiety, and anticonvulsant agent and has positive effects on cognitive function and improvement of depressive symptoms. Although safranal also helps modulate oxidative stress, this role is less prominent compared to crocin. Also, limited studies have shown the potential of safranal in cancer treatment, especially against leukemia; however, its anticancer mechanisms have been less studied compared to crocin [96-98].

Conclusion

Crocin's diverse pharmacological effects make it a promising candidate for therapeutic applications across various medical fields. Ongoing research continues to explore its mechanisms of action and potential benefits, particularly in neuroprotection and cancer treatment. As studies progress, crocin may become an integral part of strategies aimed at managing chronic diseases and improving overall health outcomes. Furthermore, its ability to modulate inflammatory responses and oxidative stress highlights its relevance in conditions such as cardiovascular diseases and metabolic disorders like diabetes and obesity. The compound's relatively safe profile at therapeutic doses further supports its potential as a functional food ingredient or dietary supplement. With increasing evidence of its efficacy, crocin could pave the way for novel treatment protocols that leverage natural compounds for enhanced health benefits, ultimately contributing to a more holistic approach to disease management and prevention. Continued investigation into its pharmacokinetics, optimal dosing, and long-term effects will be essential to fully harness crocin's therapeutic potential and integrate it effectively into clinical practice.

Highlights

What Is Already Known?

Crocin, a bioactive compound derived from saffron (Crocus sativus), has garnered considerable attention for its wide-ranging pharmacological properties. It is recognized for its neuroprotective, anti-inflammatory, and anticancer effects, showing promise in the treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's. Additionally, crocin exhibits strong antioxidant activities, which protect various tissues, including the brain, heart, and kidneys. Its cardioprotective effects are evident through improvements in cardiovascular health, such as reductions in blood pressure and enhanced endothelial function. Previous research has also indicated crocin's effectiveness in managing metabolic disorders and improving memory function, while clinical trials have shown it to be generally safe for consumption at therapeutic doses.

What Does This Study Add?

This study provides a comprehensive review of crocin's diverse pharmacological effects, synthesizing recent findings on its mechanisms of action and therapeutic potential. It highlights crocin's role in enhancing glycemic control, protecting against ischemia/reperfusion injury, and improving cognitive functions. Moreover, the research underscores crocin's potential in mitigating chemotherapy-related side effects and its renal protective effects, while addressing possible adverse effects and food/drug interactions. The study also explores innovative pharmaceutical formulations aimed at enhancing crocin's bioavailability and therapeutic efficacy, and compares its effects with those of safranal, another active component of saffron. Overall, it emphasizes crocin's potential as a functional food ingredient or dietary supplement, suggesting its integration into clinical practice for managing chronic diseases.

Authors' Contributions

AA and MMAB conceived and designed the study, conducted research, and collected and organized data. AA, MMAB, and MS wrote the initial and final draft of the article and provided logistic support. All authors have critically reviewed and approved the final draft.

Competing Interests

None.

Acknowledgments

We would like to express our gratitude to the Clinical Research Development Unit of Baqiyatullah Al-Azam Hospital.

Ethical Approval

Not applicable.

Funding

None.

Consent For Publication

Not applicable

The extent of AI use

Not applicable

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