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Crocin as an immunomodulator: Cytokine signatures and oxidative-inflammatory crosstalk

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ABSTRACT

Immune dysregulation triggers numerous pathologies, including chronic inflammation, autoimmunity, and immunodeficiency. Immunomodulators return immune balance by suppressing, stimulating, or reprogramming immune responses. Crocin, a bioactive carotenoid from *Crocus sativus* L. (saffron), exhibits broad immunomodulatory, anti-inflammatory, and antioxidant properties, offering a potential alternative to synthetic immunomodulators with adverse side effects. This review synthesizes evidence on crocin's immunomodulatory effects, primarily from experimental models, focusing on its impact on inflammatory mediators, cytokines, and immune cell activity. A literature search was conducted in the Web of Science and PubMed databases from 2001 to 2026 to identify studies evaluating crocin's effects on immune markers *in vitro* (using immune cells and tissues) and *in vivo* (in human and animal models). Analyzed biomarkers included cytokines (e.g., TNF-α, IL-6, IL-10), enzymes (e.g., iNOS, COX-2), oxidative stress markers (e.g., MDA, ROS), and signaling pathways (e.g., NF-κB, TLRs). Crocin modulates macrophage polarization, suppresses neutrophil infiltration, and regulates lymphocyte proliferation. It enhances dendritic cell maturation and mesenchymal stem cell anti-inflammatory cytokine secretion. Crocin reduces pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) in serum, brain, liver, lung, kidney, and joints. It attenuates oxidative stress and the NF-κB activation systemically. Crocin demonstrates pleiotropic immunomodulatory effects across diverse pathologies, supporting its therapeutic potential for immune-related disorders. Further clinical studies are warranted to validate its efficacy and safety in humans.

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Introduction

Dysregulation of the immune system can lead to severe health complications, including autoimmunity, chronic inflammation, and immunodeficiency (1). Immunomodulators, natural or synthetic compounds, are therapeutic agents designed to restore immune homeostasis. These substances modulate immune activity by stimulating, suppressing, or reprogramming immune responses (2). In immunodeficiency disorders such as AIDS, immunostimulants (e.g., IL-7 or checkpoint inhibitors) can enhance immune function, reducing morbidity and mortality (3, 4). Conversely, in autoimmune diseases, allergies, or organ transplantation, immunosuppressants (e.g., Tumor necrosis factor-α (TNF-α) inhibitors or Janus kinase (JAK) inhibitors mitigate harmful immune responses (5). For chronic infections (e.g., hepatitis B or tuberculosis), immunomodulators help restore immune competence, preventing organ failure and death. By recalibrating immune responses, these therapies have transformed outcomes for conditions that once led to irreversible disability or fatal organ dysfunction (4, 6).

Cytokines are potent signaling proteins produced by various cell types, particularly immune cells, that mediate intercellular communication. These molecules coordinate critical physiological processes, including the regulation of systemic and local inflammation, cell proliferation, metabolism, and tissue repair. A key function of cytokines is to modulate immune responses in both health and disease. Cytokines are generally classified as pro-inflammatory (e.g., Interleukin (IL)-1β, IL-6, IL-8, IL-12, IL-17, IL-18, IL-23, TNF-α, and IFN-γ) or anti-inflammatory (e.g., IL-4, IL-5, IL-10, IL-13, and Transforming Growth Factor (TGF)-β). However, some cytokines may exhibit context-dependent immunomodulatory functions. Specific cell populations secrete each cytokine in response to stimuli such as pathogens, tissue damage, or other cytokines.

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Upon binding to their cognate receptors, cytokines trigger signaling cascades that modulate transcription factors and gene expression, ultimately influencing cellular function. This may result in further cytokine secretion, up-regulation of surface receptors, or feedback inhibition to terminate the response. Following immunomodulator administration, shifts in the cytokine profile (e.g., increased IL-10/TGF-β or suppressed IL-6/TNF-α) can indicate whether the immune response is skewed toward anti-inflammatory or pro-inflammatory outcomes (7, 8).

Crocus sativus L. (saffron), a renowned member of the *Iridaceae* family, is cultivated worldwide, with Iran being one of its primary producers (9). With a history spanning millennia, saffron has been widely used in traditional medical systems across various cultures (10, 11). Modern pharmacological studies have validated its traditional uses in treating ocular disorders (conjunctivitis, cataracts), respiratory conditions, and gastrointestinal ailments (12). The therapeutic properties of saffron are primarily attributed to its major bioactive constituents, including crocin (a water-soluble apocarotenoid pigment), crocetin (an apocarotenoid dicarboxylic acid), and safranal (a volatile monoterpene aldehyde) (13).

Crocin is a water-soluble glycosylated apocarotenoid consisting of crocetin esterified with two gentiobiose residues (13). Extensive pharmacological research has demonstrated crocin's multifaceted therapeutic potential, including antidepressant effects (14), cardioprotective properties (anti-atherosclerotic and anti-platelet aggregation) (15, 16), anti-inflammatory (17, 18), analgesic activities (19, 20), anti-tumor effects (21), and neuroprotective actions in Alzheimer's and Parkinson's diseases (22, 23). Given the significant side effects of synthetic immunomodulators (e.g., corticosteroids, calcineurin inhibitors), there is growing interest in plant-derived alternatives like crocin for their superior safety profiles and pleiotropic mechanisms of action (24).

The present review synthesizes experimental and clinical evidence to delineate crocin's immunomodulatory mechanisms at the molecular, cellular, and organ levels. Special emphasis is placed on cytokine regulation, oxidative-inflammatory crosstalk, and context-dependent immune recalibration. By integrating data from *in vitro* systems, animal models, and human studies, this review aims to clarify how crocin orchestrates immune responses under diverse pathological conditions and to identify potential therapeutic implications for immune-related disorders.

Method

This study was conducted as a structured narrative review. A systematic literature search was conducted in PubMed and Web of Science to identify original research articles published between January 2001 and April 2026 that investigated the immunomodulatory effects of crocin. These databases were selected due to their extensive coverage of biomedical and immunological research.

The search strategy combined controlled vocabulary terms (MeSH in PubMed) and free-text keywords using Boolean operators as follows: ("crocin") AND ("immunomodulation" OR "immune modulation" OR "immune response" OR "immune regulation" OR "inflammation" OR "anti-inflammatory" OR "cytokine" OR "inflammasome" OR "oxidative stress" OR "macrophage" OR "T cell" OR "lymphocyte").

Studies were included if they:

1) quantitatively evaluated crocin's effects on immune function;
2) measured cytokines, inflammatory mediators, immune cell phenotypes, and signaling pathways;
3) were conducted in *in vitro* systems, animal models (mice or rats), or human clinical settings;
4) were published in peer-reviewed English-language journals.

Studies were excluded if they were review articles, conference abstracts, editorials, non-English publications, or did not specifically evaluate immune-related endpoints.

All titles and abstracts were screened for relevance, followed by full-text evaluation of eligible articles. Reference lists of selected studies were manually reviewed to identify additional relevant publications. After removing duplicates and non-eligible studies, a total of 95 articles were included in the final analysis.

Immunomodulatory effects of crocin on different innate and acquired immune system cells

Macrophage

Peritoneal macrophages collected from crocin-treated mice showed a significant increase in *ex vivo* yeast phagocytosis capability (25). Crocin also demonstrates significant regulatory effects on macrophage polarization, shifting the balance from pro-inflammatory M1 to anti-inflammatory M2 phenotypes. In murine cell line models of inflammation (induced by lipopolysaccharide (LPS) or titanium particles), crocin treatment down-regulated M1 markers; Cluster of Differentiation (CD)16/32, CD86, Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B-cells (NF-κB) p65, and inducible nitric oxide synthase (iNOS), TNF-α, and IL-1β, while up-regulated M2 markers; CD206 and Arginase (Arg)-I (26-28). In concurrent treatment with LPS and INF-γ, crocin could halt the rise in M1 markers (iNOS/ Arg-I ratio and TNF-α secretion) in J774.A1 mouse macrophages (29). It was found that M2 peptide-targeted liposomes containing crocin significantly shifted the phenotype of tumor macrophages towards an anti-tumor M1 phenotype in the C26 colon carcinoma xenograft mouse model (30). Similar effects were observed in rat models of vitamin D3-induced coronary atherosclerosis, in which crocin suppressed M1-associated markers such as CD40 and CD11C while enhancing the M2 marker CD206 (16).

These findings suggest that crocin acts as an immunomodulator rather than a generalized immunosuppressive agent. In addition to suppressing excessive M1-driven inflammatory responses, crocin enhanced macrophage phagocytic activity, indicating preservation of antimicrobial defense functions. Moreover, the effects of crocin on macrophage polarization appear to be microenvironment-dependent, promoting anti-inflammatory M2 phenotypes in inflammatory disorders while favoring anti-tumor M1 polarization in a cancer model. These observations indicate that crocin may contribute to the restoration of immune homeostasis by balancing pathogen defense and inflammation-induced tissue injury (Table 1).

Dendritic cells (DCs)

A study demonstrates that crocin promotes the proliferation and maturation of DCs derived from bone marrow in pediatric acute leukemia models. Crocin-treated DCs improved T-cell stimulatory capacity (31) (Table 1).

Neutrophils

Crocin has demonstrated significant anti-inflammatory effects on neutrophil activity in preclinical models and in rat studies of histamine- and carrageenan-induced acute inflammation (Table 1). Crocin treatment effectively reduced neutrophil infiltration into paw tissues, diminished

Table 1. Immunomodulatory effects of crocin on different innate and acquired immune system cells

Type of immune cell	Subject	Pathological condition	Dose or concentration/ route/ duration of administration	Effect	Ref.
Macrophage	Mouse (Swiss albino)	*Ex vivo*-yeast treatment	1, 1.5, and 2 mg/kg/day PO for 5 days	↑Peritoneal macrophage yeast-phagocytic ability	(25)
	Mouse cell line (C57BL/6)	Titanium particle (0.1 mg/ml) -treated RAW264.7 cell line	40 and 80 µM, for 24 hr	↓TNF-α, ↓IL-6, ↓M1 marker, including: CD86, iNOS ↑M2 Markers, including: CD206, Arg-I ↑IL-4, ↑IL-10	(26)
	Mouse cell line (BALB/c)	LPS-treated BV-2 microglial cell line	5-20 µM 30 min before stimulation with LPS for 24 hr	↓TNF-α ↓IL-1β ↓NO ↓ROS ↓M1 markers including iNOS, NF-κBp65, and CD16/32 ↑ M2 marker including CD206	(27)
	Mouse cell line (C57BL/6)	LPS-treated BV-2 microglial cell line	0.1-10 µM 1 h before stimulation with LPS	↓Microglial markers (CD11b and Iba-1) ↓iNOS ↓COX-2 ↓IL-1β ↓TNF-α	(28)
	Mouse cell line (BALB/c)	LPS / INF-γ -treated J774A.1 cell line	25-100 µM concurrent treatment for 24 hr	↓ M1 Markers including: iNOS/Arg-I ratio, ↓TNF-α	(29)
	Mouse (BALB/c)	Tumor-associated macrophages of the C26 colon carcinoma cell line-xenograft model	f2-targeted nanoliposomes of crocin at a dose of 50 mg/kg (IV) every other day for two months	↑ ratio of CD86 (M1 marker) to CD163 (M2 marker)	(30)
	Rat (Wistar)	Rat coronary atherosclerosis induced by vitamin D3	100 mg/kg/day PO for 4 weeks	↓M1 markers including CD40 and CD11c ↓NF-κB ↑M2 marker, including CD206	(16)
DC	Human	Isolated DC derived from the bone marrow of children with acute leukemia treated with Recombinant human (rh)GM-CSF, rhIL-4, and rhTNF-α	0.3125, 1.25, or 5.0 mg/ml for 9 days	↑DC proliferation and the enhancement of the proliferation of T cells by them	(31)
Neutrophil	Rat (Wistar)	Paw edema neutrophil infiltration induced with histamine 0.1%	100, and 200 mg/kg IP 30 min before intraplantar injection of histamine	↓Paw thickness ↓Infiltration of neutrophils in paw tissues	(32)
	Rat (Wistar)	Paw edema and neutrophil infiltration induced by carrageenan	25, 50, and 100 mg/kg IP 30 min before intraplantar injections of carrageenan	↓Edema ↓Inflammatory pain responses ↓Infiltration of neutrophils in paw tissues	(17)
Lymphocyte	Human B lymphocyte cancer cell line	U266 myeloma cell line	250, and 500 µM for 24 and 48 hr	↓B-cell viability and proliferation (mildly) ↑B-cell apoptosis and DNA fragmentation (mildly) No change in HSP 70 and 90	(33)
	Human T cells	T lymphocyte cells isolated from the peripheral blood of children with acute lymphoblastic leukemia	0.625 2.5 mg/ml for 72 hr	↑T-cell proliferation ↑IL-2 ↑IL-4 ↑CD4/CD8 ratio of the T subset ↓DNA damage in T-cells treated with Ara-C	(34)

Continued Table 1.

Human cells	Isolated PBMC cells, including T-lymphocytes (~ 70%)	25 µM for 72 hr	↓ ratio of IFN-γ/IL-4 and T-bet/GATA-3 induced by ConA.	(35)
Mouse (Nc/Nga)	Atopic dermatitis symptoms induced by *Dermatophagoides farinae* crude extract	100 mg (0.1 and 0.3%) topical application for 3 weeks	↓ thymus and activation-regulated chemokines ↓IL-4 ↓IL-13 ↓Th2 cell-mediated immune response	(36)
Mouse (C57BL/6)	Autoimmune encephalomyelitis (a murine model of MS)	25 µM	↓T-cell proliferation Inducing regulatory T cell responses ↓Proinflammatory cytokines ↑Anti-inflammatory cytokines	(37)

Cytarabine: Ara-C; Arg-I: Arginase-1; CD: Cluster of differentiation; COX-2: Cyclooxygenase-2; ConA: Concanavalin A; DC: Dendritic cells; GM-CSF: Granulocyte macrophage colony-stimulating factor; GATA-3: GATA-binding factor 3; IFN-γ: Interferon gamma; IL: Interleukin; iNOS: Inducible nitric oxide synthase; IP: Intraperitoneal; LPS: Lipopolysaccharide; M1: Pro-inflammatory macrophage; M2: Anti-inflammatory macrophage; MS: Multiple Sclerosis; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B-cells; NO: Nitric oxide; PO: Per Oral; PBMC: Peripheral blood mononuclear cells; rh: Recombinant human; ROS: Reactive oxygen species; T-bet: T-box transcription factor; TNF-α: Tumor necrosis factor-alpha

edema formation, and lowered myeloperoxidase (MPO) activity, a key marker of neutrophil activation (17, 32).

B and T lymphocytes

Crocin exhibited dose-dependent immunomodulatory effects on lymphocyte populations (Table 1). High concentrations (≥50 µM) of crocin induced mild apoptosis in U266 human myeloma cells (33). Crocin enhanced the $CD4^+/CD8^+$ ratio and proliferation in pediatric Acute Lymphoblastic Leukemia (ALL)-derived T-cells (34). When human lymphocytes were treated with Concanavalin A (a well-known activator and stimulator of Th1 cells) and crocin concurrently, crocin alleviated the inflammation-triggering effects of Concanavalin A (ConA) on the cells through decreasing T-box transcription factor (T-bet)/GATA-binding factor 3 (GATA-3) and IFN-γ/IL-4 ratios, and restoring the balance of Th1/Th2 responses (35). Crocin repressed Th2 responses in a mouse model with atopic dermatitis by suppressing NF-κB/ Signal Transducer and Activator of Transcription (STAT)6 signaling pathways (36). It attenuated T cell proliferation and modulated cytokine production in experimental autoimmune encephalomyelitis (a murine model of Multiple Sclerosis (MS)), promoting an anti-inflammatory cytokine profile while suppressing pro-inflammatory cytokines, favoring regulatory T cell responses (37).

Overall, the collected evidence indicates that crocin exerts broad and context-dependent immunomodulatory effects across innate and adaptive immune cells. It enhances macrophage phagocytic activity while reprogramming macrophage polarization toward a predominantly anti-inflammatory M2 phenotype by suppressing NF-κB–driven M1 signaling. Crocin also supports dendritic cell maturation and T-cell stimulatory capacity, while attenuating excessive neutrophil activation and tissue infiltration in acute inflammatory settings. In lymphocyte populations, it regulates T- and B-cell responses in a dose- and disease-dependent manner by restoring Th1/Th2 balance, modulating cytokine production, and promoting regulatory immune profiles, collectively highlighting crocin as a pleiotropic immunoregulatory agent capable of fine-tuning both innate and adaptive immune responses.

The principal immune cells and signaling pathways involved in crocin-mediated immunomodulation are summarized schematically in Figure 1.

Immunomodulatory effects of crocin on different tissues/organs

The systemic effects and organ-specific immunomodulatory and protective effects of crocin across different experimental disease models are summarized in Figure 2.

Serum and plasma

In human studies, crocin treatment significantly reduced elevated serum levels of IL-17, IL-6, and TNF-α in MS and polycystic ovary syndrome (PCOS) (38, 39). Supplementing the MS patients with crocin for 8 weeks significantly lowered high-sensitivity C-reactive protein (hs-CRP) levels, suggesting that crocin may keep promise in attenuating inflammation (40).

Crocin also lowered inflammatory cytokines such as IL-6, IL-1β, and TNF-α in the serum of mouse models with dextran sodium sulfate (DSS)-stimulated ulcerative colitis (UC) and caecal ligation and puncture (CLP)-induced sepsis (41, 42). In murine RA models, crocin significantly reduced plasma levels of TNF-α, IL-6, and IL-1β, attenuating joint inflammation and cartilage degradation (43). In addition, the anti-inflammatory effects of crocin in rats with metabolic syndrome were shown through the reduction of serum TNF-α and inflammatory cells (44).

In streptozotocin (STZ)-induced diabetic rats, crocin lowered plasma TNF-α and IL-1β levels, improving insulin sensitivity and pancreatic β-cell function (45). These findings highlight crocin's potential as a multi-targeted immunomodulator for diverse inflammatory conditions.

Crocin significantly reduced systemic Th2-associated inflammatory mediators, including serum OVA-specific IgE in an ovalbumin-induced asthma model and serum IgE levels in a Dermatophagoides farinae extract-induced atopic dermatitis model (36, 46).

Collectively, these findings demonstrate that crocin exerts broad systemic immunomodulatory and anti-inflammatory effects by suppressing circulating pro-inflammatory cytokines and Th2-associated mediators across a wide range of inflammatory, autoimmune, metabolic, and allergic disorders. The ability of crocin to reduce serum and plasma levels of TNF-α, IL-1β, IL-6, IL-17, hs-CRP, and IgE suggests that its therapeutic effects are mediated, at least in part, by attenuating systemic inflammatory responses and restoring immune homeostasis (Table 2).

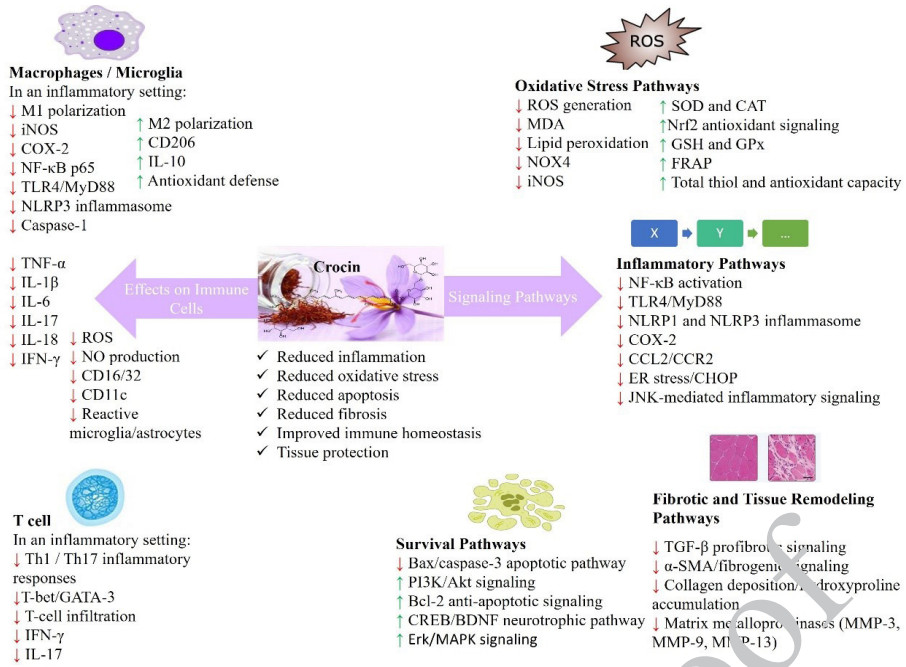

Figure 1. Effects of Crocin on Immune Cells and Signaling Pathways
Crocin modulates immune cell function (left panel) and regulates multiple interconnected signaling pathways involved in inflammation, oxidative stress, fibrosis, apoptosis, and cell survival (right panel). α-Smooth muscle actin (α-SMA), B-cell lymphoma 2 (Bcl-2), Bcl-2 associated X protein (Bax), Brain-derived neurotrophic factor (BDNF), C-C motif chemokine ligand 2/C-C chemokine receptor type 2 (CCL2/CCR2), Catalase (CAT), Caspase-1, Caspase-3, Cluster of differentiation 16/32 (CD16/32), Cluster of differentiation 206 (CD206), Cyclooxygenase-2 (COX-2), Cyclic AMP response element-binding protein (CREB), Endoplasmic reticulum (ER), Extracellular signal-regulated kinase/Mitogen-activated protein kinase (Erk/MAPK), Ferric reducing antioxidant power (FRAP), Glutathione (GSH), Glutathione peroxidase (GPx), Inducible nitric oxide synthase (iNOS), Interferon gamma (IFN-γ), Interleukin (IL), c-Jun N-terminal kinase (JNK), Lipid peroxidation, Malondialdehyde (MDA), Matrix metalloproteinase (MMP), Myeloid differentiation primary response 88 (MyD88), Nicotinamide adenine dinucleotide phosphate oxidase 4 (NOX4), Nuclear factor erythroid 2–related factor 2 (Nrf2), Nuclear factor kappa B (NF-κB), Nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 1 and 3 (NLRP1 and 3), Nitric oxide (NO), Phosphatidylinositol 3-kinase/Protein kinase B (PI3K/Akt), Reactive oxygen species (ROS), superoxide dismutase (SOD), T helper 1 (Th1), T helper 17 (Th17), Toll-like receptor 4 (TLR4), Transforming growth factor beta (TGF-β), Tumor necrosis factor alpha (TNF-α).

Muscule

Osteoarthritis (OA), a common form of arthritis, involves muscle weakness and inflammation worsened by oxidative stress. Crocin demonstrates therapeutic potential for OA by modulating inflammatory responses in muscular tissue (Table 3). In rat models of meniscectomy-induced OA, crocin treatment significantly reduced IL-6 levels in affected

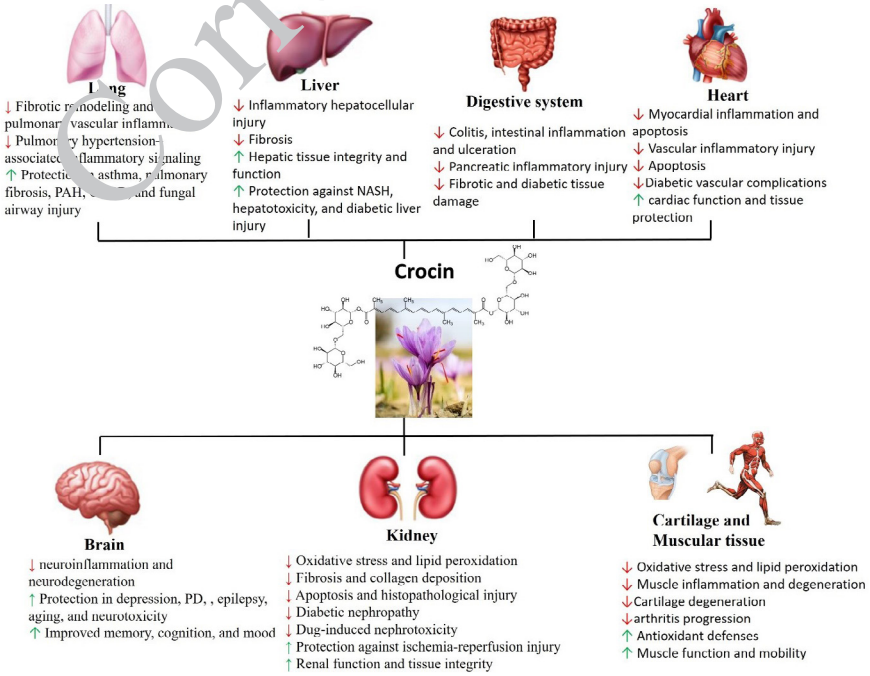

Figure 2. Protective effects of crocin across different organs and tissues
Crocin modulates key inflammatory and oxidative pathways in the brain, lung, liver, kidney, digestive system, heart, muscle, and cartilage, leading to suppression of inflammatory signaling, reduction of oxidative stress and fibrosis, preservation of tissue integrity, and improvement of functional outcomes in diverse pathological conditions. Chronic obstructive pulmonary disease (COPD), Experimental autoimmune encephalomyelitis (EAE), Pulmonary arterial hypertension (PAH), Parkinson's disease (PD)

Table 2. Immunomodulatory effects of crocin across serum and plasma

Serum/ Plasma	Subject	Pathological condition	Dose or concentration/ route/ duration of administration	Effect	Ref.
Serum	Human	MS	30 mg/day (15mg twice daily) PO for 4 weeks	↓TNF-α ↓IL-17	(38)
	Human	PCOS	15 mg, PO , twice daily for 12 weeks	↓IL-6 ↓TNF-α	(39)
	Human	MS	15 mg PO , twice daily, for 8 weeks	↓ hs-CRP	(40)
	Mouse (Swiss albino)	Oxidative damage induced by venom	Viper venoms pre-incubation with crocin (1:10; venom: crocin, w/w) at 37°C for 10 min IP	↓Venom-induced oxidative stress ↓Hematological alteration ↓IL-1β ↓TNF-α ↓IL-6	(47)
	Mouse (C57BL/6)	Metastatic mouse (induced by injecting B16F-10 melanoma cells)	250 and 500 µg/kg/day IP for 10 days	↓TNF-α ↓IL-6 ↑IL-2 ↑IL-10	(48)
	Mouse (Wistar)	Type II collagen-induced arthritis	40 mg/kg/day IP for 36 days	↓TNF-α ↓IL-6 ↓IL-17 ↓CXCL8	(49)
	Mouse (Razi)	Aging induced by d-galactose	10, 20, and 40 mg/kg/day IP for 42 days	↓TNF-α ↓IL-6	(50)
	Mouse (Nc/Nga)	Atopic dermatitis induced by Dermatophagoides farinae crude extract	100 mg (0.3% Topical application for 2 weeks	↓IgE	(36)
	Mouse (C57BL/6 J)	DSS-induced ulcerative colitis	10 and 30 mg/kg/day for 3 weeks	↓IL-1β ↓IL-2 ↓IL-6 ↓TNF-α	(41)
	Mouse (BALB/c)	OVA-induced allergic airway asthma	100 mg/kg PO 1hr before the OVA challenge	↓OVA-specific IgE	(46)
	Mouse (BALB/c)	CLP-induced sepsis in BALB/C mice	50, 100, and 250 mg/kg 30 min before CLP	↓IL-1β ↓TNF-α ↓IL-6	(42)
	Rat (Wistar)	Diazinon-induced TNF-α	50 and 100 mg/kg three times per week IP for 4 weeks	↓TNF-α	(51)
	Rat (Wistar)	FCA-induced arthritis	20 mg/kg/day PO for 2 weeks	↓TNF-α ↓IL-1β ↓IL-6	(52)
	Rat (Wistar)	FCA-induced arthritis	6.25, 12.5, and 25 mg/kg/day PO for 28 days	↓PGE2 ↓TNF-α ↓IL-1β ↓IL-6	(53)
	Rat (Wistar)	HS-operated rats	60 mg/kg, IV, right before resuscitation	↓TNF-α ↓IL-6 ↑IL-10	(54)
	Rat (Wistar)	Fructose-induced metabolic syndrome	50 mg/kg/day PO for 10 weeks	↓TNF-α	(44)
	Rat (Wistar)	Rat coronary atherosclerosis induced by vitamin D3	100 mg/kg/day PO for 4 weeks	↓TNF-α ↓IL-6 ↑IL-4 ↑IL-10 ↑TGF-β	(16)

Continued Table 2.

	Rat (Wistar)	Collagen-induced arthritis	10, 20, and 40 mg/kg/day PO for 36 days	↓TNF-α ↓IL-6 ↓IL-17 ↓CXCL8	(49)
	Rat (Wistar)	Metabolic syndrome-induced osteoporosis	5 and 10 mg/kg PO 5 days/week for 12 weeks	↓TNF-α ↓IL-6	(55)
	Rat (Swiss albino)	γ-rays- induced hepatic toxicity	200 mg/kg/day IP for 7 days before irradiation	↓TNF-α ↓IL-1β	(56)
	Rat (Wistar)	Experimentally-induced metabolic syndrome	5 and 10 mg/kg PO 5 days per week during the 12-week	↓TNF-α ↓IL-6	(57)
	Rat (Wistar)	Stress-induced kidney damage by experimental periodontitis	100 mg/kg/day PO for 15 days	↓TNF-α ↓IL-1β ↓IL-6	(58)
Plasma	Mouse	Collagen-induced arthritis	50 mg/kg/day IP for 1 week	↓TNF-α ↓IL-6 ↓IL-1β	(43)
	Rat (Wistar)	Diabetes type 2 induced by streptozocin	150 mg/kg/day PO for 6 weeks	↓TNF-α ↓IL-1β	(45)

Caecal ligation and puncture (CLP), C-X-C Motif Chemokine Ligand (CXCL), Cyclooxygenase (COX), Dextran Sodium Sulfate (DSS), Freund's Complete Adjuvant (FCA), Hemorrhagic shock (HS), High-Sensitivity C-Reactive Protein (hs-CRP), Inducible Nitric Oxide Synthase (iNOS), Interleukin (IL), Intraperitoneal (IP), Intravenous (i.v.), Immunoglobulin E (IgE), Multiple Sclerosis (MS), Ovalbumin (OVA), Per Oral (p.o.), Polycystic Ovary Syndrome (PCOS), Prostaglandin E2 (PGE2), Transforming Growth Factor (TGF), Tumor Necrosis Factor Alpha (TNF-α)

muscles, improved muscle function and mobility scores, and decreased histological markers of muscle inflammation and degeneration. It inhibited c-Jun N-Terminal Kinase (JNK) (but not Extracellular Signal-Regulated Kinase (ERK)) to block NF-κB-driven inflammation (59). Crocin lowers TNF-α, IL-6, and IL-1β in gastrocnemius muscles while boosting anti-oxidant activity (Superoxide Dismutase (SOD)1/2, catalase (CAT), and glutathione peroxidase), thereby protecting gastrocnemius muscles against damage from ischemia-reperfusion (IR) injury (60).

Cartilage

In IL-1β-stimulated rabbit chondrocytes, crocin inhibited NF-κB activation and downstream inflammatory signaling (61). Crocin suppressed pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6) and inflammatory mediators (iNOS and Toll-like receptor (TLR)2) in LPS-induced rat intervertebral disc (IVD) degeneration (18).

Inflammation and articular cartilage degeneration are the hallmarks of progressive arthritis. Crocin effectively neutralized the increased serum levels of enzymatic (Matrix Metalloproteinase (MMP)-3,-9, -13, and hyaluronidase) and non-enzymatic (IL-1β, IL-6, TNF-α, NF-κB, COX-2, and ROS) inflammatory mediators and re-established the arthritis-altered anti-oxidant status of the system (52). Similarly, in other studies, crocin exhibits therapeutic potential for collagen-induced and Complete Freund's

Table 3. Immunomodulatory effects of crocin on muscular and cartilage tissue

Organ/tissue/cell/serum	Subject	Pathological condition	Dose or concentration/ route/ duration of administration	Effect	Ref.
Muscle	Rat (Sprague-Dawley)	Osteoarthritis induced by meniscectomy	30 mg/kg/day PO for 10 days	↓ IL-6	(59)
	Rat (Sprague-Dawley)	experimental gastrocnemius muscle ischemia/reperfusion injury	60 mg/Kg IP	↓IL-6 ↓IL-1β ↑SOD1 ↑SOD2 ↑CAT ↑GPx	(60)
Cartilage	Rabbit (New Zealand) chondrocytes	IL-1β administration	5, 25, 50, and 100 μM for 24 hr	↓IL-1β-induced activation of the NF-κB pathway ↓MMP-1, -3 and -13	(61)
	Rat	FCA-induced arthritis	40 mg/kg	↓CRP ↓TNF-α ↓ IL-lβ	(62)
	Rat (Wistar)	CIA- induced arthritis	10, 20, or 40 mg/kg for 36 days	↓ TNF-α ↓ IL-17 ↓ IL-6 ↓ CXCL8	(49)
	Nucleus pulposus cells of Rat (Sprague-Dawley) IVD	LPS-administration	10, 50, and 100 μM for 7 days	↓IL-1β ↓TNF-α ↓IL-6 ↓iNOS ↓TLR-2	(18)

Colagen-Induced Arthritis (CIA), Catalase (CAT), C-Reactive Protein (CRP), Cyclooxygenase-2 (COX-2), C-X-C Motif Chemokine Ligand 8 (CXCL8), Freund's Complete Adjuvant (FCA), Glutathione Peroxidase (GPx), Interleukin (IL), Intervertebral Disc (IVD), Lipopolysaccharide (LPS), Matrix Metalloproteinase (MMP), Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B-cells (NF-κB), Inducible Nitric Oxide Synthase (iNOS), Per Os (p.o.), Reactive Oxygen Species (ROS), Toll-Like Receptor 2 (TLR-2), Superoxide Dismutase (SOD), Tumor Necrosis Factor Alpha (TNF-α)

adjuvant-induced arthritis in rats by inhibiting the pro-inflammatory factors (TNF-α, IL-17, IL-6, IL-1β, and CXCL8) in serum and ankle tissues (62).

Collectively, crocin exhibits anti-inflammatory and anti-oxidant effects in musculoskeletal tissues by attenuating oxidative stress, suppressing NF-κB–mediated signaling, and down-regulating key pro-inflammatory cytokines and mediators in muscle, cartilage, and intervertebral disc models. It improves muscle function and reduces tissue degeneration in OA and ischemia–reperfusion injury, while also inhibiting cytokines, MMPs, and inflammatory enzymes in cartilage and arthritis models, thereby protecting structural integrity and limiting progressive inflammatory damage in musculoskeletal disorders (Table 3).

Kidney

In renal ischemia/reperfusion (I/R) injury, crocin pretreatment reduced leukocyte infiltration, intercellular adhesion molecule-1 (ICAM-1), tumor necrosis factor-α (TNF-α), malondialdehyde (MDA), plasma creatinine, and blood urea nitrogen, while restoring anti-oxidant capacity, indicating attenuation of inflammatory and oxidative renal damage (63). Similarly, in infrarenal aortic occlusion-induced renal I/R injury, crocin decreased pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, IL-18, and interferon-γ (IFN-γ), reduced the oxidative stress index, Bax, caspase-3, and histopathological injury, and increased the anti-apoptotic marker Bcl-2, demonstrating anti-inflammatory and anti-apoptotic activities (64).

In diabetic nephropathy (DN), crocin ameliorated hyperglycemia-associated renal dysfunction by reducing serum creatinine, blood urea nitrogen, proteinuria, lactate dehydrogenase (LDH), nitric oxide synthase (NOS), Toll-like receptor 4 (TLR4), IL-6, and nuclear factor kappa-B (NF-κB/p65) signaling, while enhancing anti-oxidant defenses including superoxide dismutase (SOD), glutathione (GSH), and CAT activity (65). Crocin also suppressed renal fibrosis by reducing transforming growth factor-β (TGF-β), collagen deposition, and hydroxyproline accumulation, while preserving renal histological architecture (65). Another study demonstrated that crocin improved diabetic renal injury by down-regulating NADPH oxidase-4 (NOX-4), IL-18, and p53 expression, thereby attenuating oxidative stress, inflammation, apoptosis, and histopathological damage (66). In addition, crocin has been reported to alleviate oxidative stress and inflammatory responses associated with diabetic nephropathy by inhibiting activation of the NLR Family Pyrin Domain-Containing Protein 3 (NLRP3) inflammasome (67).

Crocin also protected against drug-induced nephrotoxicity. In doxorubicin-induced renal injury, crocin restored renal anti-oxidant defenses by increasing SOD, CAT, and GSH levels while suppressing oxidative stress, IL-1β expression, and TGF-β-mediated fibrotic signaling, ultimately improving renal morphology and function (68). Similar nephroprotective effects were observed against gentamicin-induced toxicity, where crocin decreased plasma creatinine, urea nitrogen, and MDA levels, restored ferric reducing/anti-oxidant power (FRAP), and ameliorated tubular necrosis, fibrosis, edema, and vascular congestion (69). Comparable anti-oxidant and anti-inflammatory renoprotective effects were also reported in another doxorubicin nephrotoxicity model (70).

Collectively, these findings indicate that crocin exerts broad renoprotective effects by targeting interconnected oxidative-inflammatory pathways. Across diverse renal injury models, crocin consistently suppressed pro-inflammatory cytokines, NF-κB/NLRP3-related signaling, oxidative stress mediators, fibrosis, and apoptosis while enhancing endogenous anti-oxidant defenses. These observations suggest that modulation of oxidative-inflammatory crosstalk represents a central mechanism underlying crocin-mediated

Table 4. Immunomodulatory effects of crocin on the kidney

Subject	Pathological condition	Dose or concentration/ route/ duration of administration	Effect	Ref.
Rat (Wistar)	Ischemia/reperfusion-induced renal injuries	100, 200, and 400 mg/kg IP 30 min before ischemia/reperfusion	↓TNF-α ↓ICAM-1 ↓Leukocyte infiltration	(63)
Rat (Wistar-Albino)	Ischemia/reperfusion-induced renal injuries	100 mg/kg IP	↓IL-6 ↓IL-1β ↓TNF-α ↓IL-18 ↓INF-γ	(64)
Rat	Doxorubicin-Induced Nephrotoxicity	40 mg/kg daily for 15 days	↓IL1β ↓TGF-β	(68)
Rat (albino Sprague-Dawley)	Doxorubicin-Induced Nephrotoxicity	100 mg/kg IP for 3 weeks	↓NF-κB ↓iNOS ↓COX2 ↓TNF-α ↓MDA ↓SOD	(70)
Rat (Wistar)	Renal toxicity induced by gentamicin	100 mg/kg IP for 7 days	↓Plasma creatinine ↓Urea-nitrogen ↓Oxidative stress ↓Renal MDA ↑Renal FRAP	(69)
Rat (Sprague-Dawely)	Diabetic nephropathy induced by streptozotocin	20 mg/kg PO for 8 weeks	↓Renal fibrosis ↓TLR-4 ↓IL-6 ↓NF-κB	(65)
Rat (Wistar)	Diabetic nephropathy induced by streptozotocin	40 mg/kg IP for 8 weeks	↓IL-18 ↓NOX-4	(66)
Rat (prague–Dawley)	Diabetic nephropathy induced by streptozotocin	50 mg/kg, IP daily for 8 weeks	↓TNF-α ↓IL-1β ↓IL-18 ↓NLRP3 inflammasomes	(67)

COX2: Cyclooxygenase-2; FRAP: Ferric reducing antioxidant power; ICAM-1: Intercellular adhesion molecule 1; IL: Interleukin; INF-γ: Interferon gamma; IP: Intraperitoneal; MDA: Malondialdehyde; NOX4: NADPH oxidase 4; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B-cells; iNOS: Inducible nitric oxide synthase; p.o.: Per oral; SOD: Superoxide dismutase; TGF-β: Transforming growth factor Beta; TLR-4: Toll-like receptor 4; TNF-α: Tumor necrosis factor alpha

renal immunoprotection (Table 4).

Brain

Crocin modulated microglial polarization, decreasing M1 markers (iNOS, NF-κB p65, CD16/32) while increasing the M2 marker CD206 in the BV2 cell line (27). Antidepressant activity of crocin in a mouse model of chronic corticosterone-induced depression was associated with a decrease in IL-1β and oxidative stress in the mouse hippocampus (71).

During experimental autoimmune encephalomyelitis (EAE), daily treatment with crocin suppressed inflammatory gene expression and endoplasmic reticulum (ER) stress in spinal cords, accompanied by preserved myelination and axonal density, reduced macrophage activation, and reduced T cell infiltration (72).

Crocin attenuated cognitive impairment associated with atherosclerosis via improved neuroinflammation in a mouse model of atherosclerosis by inhibiting the increase in reactive astrocytes and microglia, weakening Caspase-1, IL-1β, NF-kB p65, and MyD88, and blocking TLR4 signaling, accompanied by a decrease in NLRP3 inflammasome activation (73).

Crocin could improve memory impairment induced by unpredictable chronic mild stress (UCMS) in Wistar rats. It decreased oxidative stress indicators MDA, nitrite, pro-inflammatory cytokine TNF-α, and amyloid-β (Aβ) (pathological hallmark of Alzheimer's disease), and glial fibrillary acidic protein (GFAP). In contrast, it increased anti-oxidant agents (total thiol content, SOD, and catalase activity) and anti-inflammatory cytokine (IL-10) (74). Crocin reduced neuroinflammation in a Parkinson's disease (PD) model by diminishing IL-1β, IL-18, Nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) protein 1 (NLRP1), Absent in melanoma 2(AIM2), and caspase-1 levels (75).

Crocin-loaded solid lipid nanoparticles had protective effects against oxidative stress in neurons, improved neurocognitive function, and exhibited anti-apoptotic and neuromodulatory activity in pentylenetetrazol-induced epilepsy in rats. It reduced MDA, caspase-3, proinflammatory and inflammatory cytokines, while increasing total anti-oxidant capacity (76).

In a D-galactose-induced aging model, crocin improved spatial learning and memory while reducing hippocampal MDA, advanced glycation end products (carboxymethyl lysine), nuclear factor kappa B (NF-κB p65), tumor necrosis factor-α (TNF-α), and IL-1β levels (77). These protective effects were associated with activation of Phosphatidylinositol 3-kinase (PI3K)/Protein kinase B (Akt) and Erk/Mitogen-Activated Protein Kinase (MAPK) signaling pathways, suggesting that crocin counteracts age-related neuroinflammation and cognitive decline through combined anti-inflammatory, anti-oxidant, and anti-glycative mechanisms (77).

In stimulant-induced neurotoxicity models, crocin exerted marked neuroprotective effects through modulation of oxidative-inflammatory pathways and neurotrophic signaling. In methylphenidate-induced neurotoxicity, crocin attenuated cognitive impairment and hyperlocomotion while decreasing lipid peroxidation, IL-1β, TNF-α, Bax, and oxidized glutathione (GSSG), and increasing reduced glutathione (GSH), anti-oxidant enzyme activities, Bcl-2, phosphorylated cyclic AMP response element-binding protein (P-CREB), and brain-derived neurotrophic factor (BDNF) levels in the hippocampus (78). Similar findings were observed in methamphetamine-induced neurodegeneration, where crocin reduced oxidative stress, inflammation, and apoptosis, while restoring CREB/BDNF signaling and improving learning and memory performance (79). These findings suggest that activation of the CREB-BDNF pathway is a major mechanism underlying crocin-mediated neuroprotection against stimulant-induced neuronal injury.

In a 6-hydroxydopamine (6-OHDA)-induced Parkinson's disease model, crocin alone or combined with treadmill exercise ameliorated motor dysfunction and memory deficits while reducing striatal TNF-α and hippocampal lipid peroxidation and enhancing anti-oxidant thiol content (80). These results indicate that crocin may protect against dopaminergic neurodegeneration through attenuation of inflammatory and oxidative stress responses (80). Moreover, crocin was also reported to reduce inflammatory responses and improve anxiety-like behaviors in amyloid-beta-induced neurotoxicity models, further supporting its beneficial role in neuroinflammatory and neurodegenerative disorders (81).

Crocin exerts broad neuroprotective and immunomodulatory effects by suppressing neuroinflammation and oxidative stress, inhibiting key inflammatory pathways (NF-κB, TLR4, inflammasomes), reducing microglial activation, and limiting apoptosis, while simultaneously enhancing anti-oxidant defenses and activating pro-survival neurotrophic signaling pathways (e.g., PI3K/Akt and BDNF-related signaling). Collectively, these actions preserve neuronal integrity and contribute to improved functional outcomes in diverse neurological

Table 5. Immunomodulatory effects of crocin on the brain

Subject	Pathological condition	Dose or concentration/ route/ duration of administration	Effect	Ref.
Mouse ($LDLR^{-/-}$)	Cognitive impairment associated with atherosclerosis in mice	High-fat/cholesterol diet + Oral gavage of crocin for 56 days	↓ Caspase-1 ↓ IL-1β ↓ NF-kB ↓ TLR4	(73)
Mouse hippocampus (C57BL/6)	LPS-induced anxiety and depressive-like behaviors in mouse	20 and 40 mg/kg IP for 1 week	↓IL-1β ↓TNF-α ↓IL-18	(27)
Mouse hippocampus (C57BL/6J)	Depression induced by corticosterone in the mouse	20 and 40 mg/kg PO for 2 weeks	↓IL-1β ↓Oxidative stress	(71)
Rat (Wistar)	Parkinson's disease model	30 mg/kg/day IP for 4 weeks	↓ IL-1β ↓ IL-18 ↓ caspase-1	(75)
Rat (Wistar)	Pentylenetetrazol - induced epilepsy	25 and 50 mg/kg/day, PO for 28 days	↓ MDA ↓ caspase-3 ↓ Proinflammatory cytokines	(76)

Continued Table 5.

Rat (Wistar)	Memory impairment induced by unpredictable chronic mild stress	10, 20, and 30 mg/kg/day	↓ MDA ↓ TNF-α ↓ Aβ ↑ SOD ↑ catalase activity ↑ IL-10	(74)
Rat (Wistar)	Brain aging and memory impairment induced by D-galactose	7.5, 15, 30 mg/kg IP for 8 weeks	In Hippocampus: ↓IL-1β ↓TNF-α	(77)
Rat (Wistar)	Methylphenidate administration	Concurrently, 10 - 80 mg/kg IP for 21 days	In Hippocampus: ↓Oxidative stress ↓Inflammation ↓IL-1β ↓TNF-α ↓Apoptosis	(78)
Rat (Wistar)	Methamphetamine-induced Neurodegeneration	Concurrently, 40 and 80 mg/kg IP for 21 days	In Hippocampus: ↓Oxidative stress ↓Inflammation ↓IL-1β ↓TNF-α ↓Apoptosis	(79)
Rat (Wistar)	Hemiparkinson induced by the neurotoxin 6-hydroxydopamine	100 mg/kg IP for 6 weeks	↓TNF-α in the striatum	(80)
Rat (Wistar)	Amyloid-beta induced neurotoxicity	30 mg/kg IP daily up to 12 days	Hippocampus: ↓IL-1β ↓TNF-α	(81)

Amyloid-beta (Aβ), Interleukin (IL), Intraperitoneal (IP), Lipopolysaccharide (LPS), Malondialdehyde (MDA), Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B-cells (NF-kB), Per Oral (P.O.), Superoxide Dismutase (SOD), Toll-Like Receptor 4 (TLR4), Tumor Necrosis Factor Alpha (TNF-α).

disorders (Table 5).

Lung

In *Aspergillus fumigatus*-infected bronchial epithelial cells, crocin suppressed IL-1β, IL-6, IL-8, and TNF-α by inhibiting NF-κB (82).

In OVA-induced murine asthma models, crocin alleviated airway inflammation and oxidative stress by reducing Th2 cytokines (IL-4 and IL-13) and lipid peroxidation while enhancing anti-oxidant defenses, including SOD, CAT, and GSH. Crocin also improved lung histopathological changes and suppressed ER stress- and apoptosis-related markers such as CHOP and caspase-12, indicating that its anti-asthmatic effects are mediated through modulation of oxidative stress and ER stress pathways (83, 84). In bleomycin (BLM)-induced pulmonary fibrosis models, it was reported that crocin attenuated TGF-β1, TNF-α, TLR-4, and oxidative markers (MDA, NO) (85, 86).

Inflammation plays a vital role in the occurrence and progression of pulmonary arterial hypertension (PAH) as a malignant cardiopulmonary disease. It has been shown that crocin decreased inflammatory cell infiltration, expression of the CCL2/CCR2 inflammatory pathway, inflammatory cytokines, and oxidative stress responses, and finally significantly reduced pulmonary arterial systolic pressure and mean pulmonary artery pressure in PAH rat models (87). Inflammation and oxidative stress affect the pathophysiology of chronic obstructive pulmonary disease (COPD). Administration of crocin for 12 weeks in COPD patients could lower serum levels of IL-6 and TNF-*α*, which caused an improvement in exercise capacity and pulmonary function tests in these patients (88).

Overall, the available evidence indicates that crocin exerts broad protective effects in pulmonary disorders through coordinated anti-inflammatory, anti-oxidant, antifibrotic, and ER stress–modulating mechanisms. Across experimental models of fungal airway infection, asthma, pulmonary fibrosis, PAH, and COPD, crocin consistently attenuated inflammatory cytokine production, oxidative stress, inflammatory cell infiltration, and profibrotic signaling pathways, leading to improved pulmonary and cardiopulmonary function. These findings support the therapeutic potential of crocin as a multifunctional agent targeting key pathological processes involved in both acute and chronic lung diseases (Table 6).

Table 6. Immunomodulatory effects of crocin on the lung

Subject	Pathological condition	Dose or concentration/ route/ duration of administration	Effect	Ref.
Human	COPD	15 mg twice a day for 12 weeks	↓ Exercise capacity ↓PFT In serum: ↓ IL-6 ↓ TNF-*α*	(88)
Human bronchial epithelial cells (BEAS-2B and NHBE)	*Aspergillus* induced inflammation	0.1, 1, and 10 μM pretreatment for 24 hr	↓TNF-α ↓IL-1β ↓IL-8 ↓IL-6	(82)
Mouse (BALB/C)	OVA-induced allergic airway asthma	100 mg/kg PO 1 hr before the OVA challenge	↓IL-4 ↓IL-5 ↓IL-13 ↓Tryptase ↓Eotaxin	(46)

Continued Table 6.

Mouse	OVA-sensitized mice	25, 50, and 100 mg/kg PO 1h before the OVA challenge	↓IgE ↓CHOP ↓TNF-α ↓IL-1β ↓IL-6 ↓Caspase 12	(84)
Mouse (Swiss albino)	OVA-induced allergic airway asthma	25 mg/kg/day PO for 16 days	↓IL-4 ↓IL-13	(83)
Rat	Monocrotaline-Induced Pulmonary arterial hypertension	Gastric tube daily for four weeks	↓ Inflammatory cell infiltration ↓ Inflammatory cytokines ↓ Oxidative stress responses ↓CCL2/CCR2	(87)
Rat (Sprague-Dawley)	BLM-induced pulmonary fibrosis	20 mg/kg PO one week before and 4 weeks post BLM installation	↓TLR-4 ↓TNF-α ↓TGF-β1	(85)
Rat (Wistar)	BLM-induced pulmonary fibrosis	25 mg/kg/day PO for 28 days	↓TNF-α ↓MDA ↓NO ↑GSH ↑CAT ↑GPx	(86)

Bleomycin (BLM), Catalase (CAT), C/EBP Homologous Protein (CHOP), Chronic Glutathione (GSH), Glutathion Peroxidase (GPx), Obstructive Pulmonary Disease (COPD), Immunoglobulin E (IgE), Interleukin (IL), Malondialdehyde (MDA), Nitric Oxide (NO), Ovalbumin (OVA), Per Oral (p.o.), Pulmonary Function Tests (PFT), Transforming Growth Factor Beta 1 (TGF-β1), Toll-Like Receptor 4 (TLR-4), Tumor Necrosis Factor Alpha (TNF-α).

Liver

In thioacetamide-induced liver fibrosis and nonalcoholic steatohepatitis (NASH) mouse models, crocin treatment significantly reduced hepatic TNF-α levels and inhibited NF-κB activation and downstream pro-inflammatory signaling (89, 90). In methotrexate-, cisplatin-, and ethanol-induced hepatotoxicity, crocin decreased hepatic TNF-α, IL-1β, TGF-β, and IL-6 (91-93). Crocin attenuated pro-inflammatory cytokines, NF-κB, IL-6, TNF-α, fibrogenic factor, TGF-β, and α-smooth muscle actin, which caused inhibition of liver fibrosis progression induced by carbon tetrachloride (94). It decreased the levels of inflammatory factors in the diabetic mice with inflammation in hepatocytes due to high levels of methylglyoxal (95). Crocin showed protective effects against liver tissue damage in pinealectomized diabetic rats by decreasing IL-1β and MDA and increasing anti-oxidant enzyme levels and tissue total anti-oxidant status (96).

Collectively, the available evidence indicates that crocin exerts substantial hepatoprotective and immunomodulatory effects through coordinated suppression of inflammatory, oxidative, and fibrotic pathways. Across diverse models of liver injury, including fibrosis, nonalcoholic steatohepatitis, drug-induced hepatotoxicity, diabetic hepatic inflammation, and ethanol-induced damage, crocin consistently reduced pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, while inhibiting NF-κB and TGF-β-mediated profibrotic signaling. In parallel, crocin enhanced anti-oxidant defenses and attenuated lipid peroxidation, contributing to the preservation of hepatic architecture and function. These findings suggest that modulation of oxidative-inflammatory-fibrotic crosstalk is a central mechanism underlying crocin-mediated protection against acute and chronic liver injury (Table 7).

Table 7. Immunomodulatory effects of crocin on the liver

Subject	Pathological condition	Dose or concentration/ route/ duration of administration	Effect	Ref.
Mouse (SWR)	Liver fibrosis induced by thioacetamide	25 and 100 mg/kg PO for 6 weeks	↓NF-κB ↓COX-2 ↓TGF-β ↓IL-1β ↓TNF-α	(89)
Mouse (NMRI)	NASH model mice	100 mg/kg twice a week, for 3 weeks	↓caspase 3 ↓NF-κB ↓TNF-α	(90)
Mouse (NMRI)	Methylglyoxal-induced diabetes	60 mg/kg/day, PO for 2 weeks	↓ Inflammatory factors	(95)
Mouse (NMRI)	Acrylamide-Induced Hepatic Injury	50 mg/kg orally for 2 weeks	↓IL-6 ↓TNF-α	(97)
Rat (Wistar)	Methotrexate- induced hepatotoxicity	25 and 50 mg/kg PO for 9 days	↓ TNF-α ↓ IL-1β ↓Oxidative stress	(91)
Rat (Wistar)	Cisplatin-induced hepatotoxicity	200 mg/kg IP for 7 days	↓TGF-β ↓NF-κB ↓TLR-4 signaling	(92)

Continued Table 7.

Rat (Wistar)	Ethanol- -induced hepatotoxicity	10, 20, and 40 mg/Kg IP for 4 weeks	↓TNF-α ↓IL-6 ↓MDA	(93)
Rat (Wistar)	Carbon tetrachloride-induced liver fibrosis	20, 40, and 80 mg/kg, PO, for 8 weeks	↓ NF-κB ↓ IL-6 ↓ TGF-β	(94)
Rat (Wistar)	Carbon tetrachloride-induced liver fibrosis	100 mg/kg/day IP for 2 weeks	↓TGF-β ↓ TNF-α ↓ IL-1β ↓ NO	(98)
Rat	STZ-induced diabetes in pinealectomized rat	50 mg/kg, IP for 15 days	↓ IL-1β ↓ MDA ↑ Anti-oxidant enzyme	(96)

Cyclooxygenase-2 (COX-2), Interleukin (IL), Malondialdehyde (MDA), Non-Alcoholic Steatohepatitis (NASH), Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B-cells (NF-κB), Nitric Oxide (NO), Per Oral (p.o.), Streptozotocin (STZ), Transforming Growth Factor Beta (TGF-β), Toll-Like Receptor 4 (TLR-4), Tumor Necrosis Factor Alpha (TNF-α).

Digestive system

In HCT116 human colon cancer cells, crocin treatment significantly reduced pro-inflammatory cytokines IL-8, IL-6, IL-1β, chemokines like macrophage inflammatory protein 2 (MIP2), monocyte chemoattractant protein 1 (MCP-1), and activation of inflammatory mediator NF-κB (99). Crocin attenuated inflammatory cytokines (IL-1β, IL-6, and IL-17), enzymes (iNOS and COX-2), and DSS-induced ulcerative colitis (41). It reduced oxidative stress markers (MDA and SOD) and also suppressed TNF-α in rat colitis models (100). Crocin showed a protective effect against indomethacin-induced intestinal ulcer by increasing superoxide dismutase (SOD) activity and decreasing organo-somatic index (OSI), MDA, TNF-α, and caspase-3 contents of intestinal tissue (101).

Pancreas

Crocin demonstrates significant anti-inflammatory and antidiabetic properties in pancreatic disorders (Table 8). In cerulein-induced acute pancreatitis (AP) mice, crocin reduced pro-inflammatory cytokines (IL-1β, TNF-α, IL-17, and IL-6), and decreased NF-κB p65 activation (102). Crocin lowered TNF-α and IFN-γ in pancreatic tissue and TNF-α and TGF-β in liver tissue in type 2 diabetes induced by streptozocin, which caused a decrease in hepatocyte degeneration and inflammatory changes, relieving hyperinsulinemia, hyperleptinemia, insulin resistance, and weight gain (45, 103). Also, crocin decreases the rate of inflammatory factors and the Bcl-2-Associated X Protein (BAX)/B-cell lymphoma (Bcl-2)2 ratio in diabetic rats receiving a single dose of alloxan (104).

Collectively, these studies demonstrate that crocin protects gastrointestinal and pancreatic tissues by suppressing inflammatory cytokines, NF-κB signaling, oxidative stress, and apoptosis. Through modulation of oxidative-inflammatory pathways, crocin attenuates intestinal inflammation, colitis, pancreatic injury, and diabetes-associated tissue damage, supporting its potential as an immunomodulatory agent in gastrointestinal and pancreatic disorders (Table 8).

Table 8. Immunomodulatory effects of crocin in the gastrointestinal tract and pancreas

Organ/tissue/ cell	Subject	Pathological condition	Dose or concentration/ route/ duration of administration	Effect	Ref.
Gastrointestinal tract	Human colon cancer cell line HCT116	Colon cancer	135 and 271 μM for 48 hr	↓MIP2 ↓IL-8 ↓MCP-1 ↓IL-6 ↓IL-1β ↓TNF-α	(99)
	Mouse (C57BL/6 J)	DSS-induced ulcerative colitis	10 and 30 mg/kg once per day for 3 weeks	↓IL-1β ↓IL-6 ↓IL-17 ↓iNOS ↓COX-2	(41)
	Rat (Wistar) colon tissue	Colitis induced by acetic acid	5, 10, and 20 mg/kg IP for 8 days	↓TNF-α ↓MDA ↓SOD	(100)
	Rat (Wistar) intestine tissue	Indomethacin-induced small intestinal ulcer	2.5,10 and 40 mg /kg IP	↓TNF-α ↓MDA ↓SOD ↓Caspase 3	(105)

Continued Table 8.

	Rat colon (Sprague Dawley)	Ulcerative colitis induced by acetic acid	20 mg/kg PO for 8 days	↑Colon anti-oxidant defenses ↑Nrf2 ↓TNF-α ↓Inflammatory response ↓Oxidative stress	(106)
Pancreas	Mouse (Swiss albino)	Acute pancreatitis induced by cerulein	30 and 100 mg/kg/day IP for 7 days before cerulean treatment	↓IL-1β ↓TNF-α ↓IL-17 ↓IL-6 ↓p65-NF-κB	(102)
	Rat (Wistar)	Diabetes induced by alloxan	50 mg/kg, IP	↓Inflammatory factors ↓ BAX/Bcl2 ratio	(104)
	Rat (Wistar)	Diabetes type 2 induced by streptozocin following a 10-week-long high-fat diet	150 mg/kg/day PO for 6 weeks	↓TNF-α ↓INF-γ	(45)

Cyclooxygenase-2 (COX2), Dextran Sodium Sulfate (DSS), Interferon Gamma (IFN-γ), Inducible Nitric Oxide Synthase (iNOS), Interleukin (IL), Intraperitoneal (IP), Malondialdehyde (MDA), Monocyte Chemoattractant Protein-1 (MCP-1), Macrophage Inflammatory Protein-2 (MIP-2), Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B-cells (NF-κB), Per Oral (p.o.), Superoxide Dismutase (SOD), Transforming Growth Factor Beta (TGF-β), Tumor Necrosis Factor Alpha (TNF-α)

Heart

In a myocarditis model induced by isoprenaline and an immune checkpoint inhibitor, crocin significantly reduced IL-1β levels and NF-κB activation, which preserved cardiac function (107, 108). Crocin has a potential protective effect on Myocardial infarction (MI) in rats through decreasing the expression levels of IL-1β, IL-6, and TNF-α, inhibiting the release of inflammatory cytokines, and reducing the apoptosis of myocardial cells (109). Crocin exhibited anti-inflammatory effects on vascular tissue. In STZ-induced diabetic rats, crocin administration reduced aortic expression of pro-inflammatory cytokines TNF-α and IL-6 (110).

Overall, the available evidence indicates that crocin exerts cardioprotective and vasculoprotective effects primarily through suppression of inflammatory cytokines, NF-κB signaling, and apoptosis. By attenuating oxidative-inflammatory injury in myocardial and vascular tissues, crocin helps preserve cardiac function and mitigate inflammatory damage in myocarditis, myocardial infarction, and diabetic vascular complications (Table 9).

Mesenchymal stem cells (MSCs)

MSCs possess significant immunomodulatory properties that make them promising candidates for treating various

Table 9. Immunomodulatory effects of crocin on the cardiovascular system

Organ/tissue	Subject	Pathological condition	Dose or concentration/ route/ duration of administration	Effect	Ref.
Heart	Mouse (Kunming)	Myocardial fibrosis induced by isoprenaline	100 and 200 mg/kg/day IP for 2 weeks	↓TNF-α ↓IL-1 ↓NF-κB ↓IL-6 ↓TLR-4	(107)
	Mouse (BALB/c)	Mouse model of Immune Checkpoint Inhibitors -related myocarditis	20, 50 mg/kg/d IP for 7-14 days	↓NLRP3 ↓Gasdermin D ↓caspase1 ↓IL-1β ↓IL-18 ↓NF-κB	(108)
	Rat (Sprague Dawley)	Myocardial Ischemia-Reperfusion Injury model	100, 200 mg/kg	↓ IL-1β ↓ IL-6 ↓ TNF-α	(109)
Abdominal aorta	Rat (Wistar)	Streptozotocin-induced diabetes	10, 20, and 30 mg/kg/day IP for 4 weeks	↓TNF-α ↓IL-6	(110)

Interleukin (IL), Intraperitoneal (IP), NLR Family Pyrin Domain-Containing Protein 3 (NLRP3), Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B-cells (NF-κB), Toll-Like Receptor 4 (TLR-4), Tumor Necrosis Factor Alpha (TNF-α).

Table 10. Immunomodulatory effects of crocin across mesenchymal stem cells, skin keratinocytes, fibroblasts, and primary retinal ganglion cells

Cell	Subject	Pathological condition	Dose or concentration/ route/ duration of administration	Effect	Ref.
Mesenchymal stem cells	Human	MSC cells derived from lipoaspirates	2.5 -50 µM for 24 h	↓IL-1β ↓IL-6 ↓IL-17 ↓IFN-γ ↑IL-4 ↑IL-10 ↑TGF-β	(111)
	Human	Adipose-derived stem cells and dental pulp-derived stem cells	---	↓Akt 1 ↓Akt2 ↓NF-κB	(112)
Keratinocytes	Human HaCaT Keratinocyte cells	TNF-α/IFN-γ-stimulated	10 µM for one hr before TNF-α/IFN-γ stimulation	↓TARC/CCL17 ↓MDC/CCL22)	(113)
Primary retinal ganglion cells	Rat (Sprague Dawley)	Oxygen and glucose deprivation/reperfusion (RIR) of cells	8-12 µM	↓sod ↓TNF-α ↓IL-1β ↓IL-6	(115)

Protein kinase B (Akt), C-C Motif Chemokine Ligand (CCL), Fibroblast-Like Synoviocyte (FLS), Interferon Gamma (IFN-γ), Interleukin (IL), Lipopolysaccharide (LPS), Macrophage-Derived Chemokine (MDC), Mesenchymal Stem Cells (MSC), Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B-Cells (NF-κB), Reactive Oxygen Species (ROS), Thymus and Activation-Regulated Chemokine (TARC), Transforming Growth Factor Beta (TGF-β), Tumor Necrosis Factor Alpha (TNF-α).

inflammatory and autoimmune diseases. Recent studies demonstrate that crocin exhibits dose-dependent effects on MSC cytokine production; at low concentrations (2.5-50 µM), crocin up-regulates anti-inflammatory cytokines (TGF-β, IL-10, and IL-4), while at higher concentrations (25-50 µM), it suppresses pro-inflammatory cytokines (IL-1β, IL-6, IL-17, and IFN-γ) in human adipose-derived MSCs (111). Crocin could control the expression of immunomodulatory-related microRNAs (Mir-126, −21, -23, and -155) and their target genes (PI3K/Akt 1 and 2/ NF-κB and p65), which play a key function in the immune regulation pathways in MSCs (112) (Table 10).

Keratinocytes

Keratinocytes play a critical role in the pathogenesis of atopic dermatitis (AD). Crocin could reduce the TNF-α / IFN-γ - induced expression of important mediators of cell migration and inflammatory pathways involved in AD, including thymus and activation-regulated chemokine (Thymus and Activation-Regulated Chemokine (TARC)/ CCL17) and macrophage-derived chemokine (MDC/ CCL22) via suppression of ERK/MAPK/NF-κB/STAT signaling pathways in human epidermal keratinocytes HaCaT cells (113). In a full-thickness burn model, crocin-laden hydroxybutyl chitosan (CRO-HBC) thermosensitive hydrogel regulated the excessive release of pro-inflammatory cytokines. It promoted angiogenesis, which resulted in commendable effectiveness for tissue regeneration (114) (Table 10).

Discussion

Immune-mediated disorders arise from dysregulated immune activity, leading to persistent inflammation, tissue injury, and progressive organ dysfunction through interconnected inflammatory and oxidative pathways (116, 117). These pathological conditions are frequently characterized by disruption of immune homeostasis, in which excessive activation of innate and adaptive immune responses promotes chronic inflammatory damage (118). Cytokines play a central role in orchestrating these immune responses, and the balance between pro-inflammatory and anti-inflammatory cytokine networks critically determines disease progression and resolution (119, 120). Therefore, modulation of cytokine signaling and immune-cell activation has emerged as a major therapeutic strategy for the management of inflammatory and autoimmune diseases (121).

Immunomodulatory agents exert their effects by regulating inflammatory signaling cascades and restoring immune equilibrium. Through selective modulation of cytokine production, oxidative stress responses, and immune-cell polarization, these compounds may attenuate pathological inflammation while preserving essential host-defense mechanisms. In recent years, naturally derived bioactive compounds have gained increasing attention as potential immunomodulatory agents because of their multitarget activities and relatively favorable safety profiles (122).

Saffron stigmas contain numerous bioactive compounds, including terpenes, flavonoids, and carotenoids. Among these, crocin is a principal apocarotenoid responsible for saffron's distinctive color and numerous pharmacological properties (123). The present review synthesized experimental and clinical evidence demonstrating that crocin exerts significant immunomodulatory effects in various inflammatory and autoimmune conditions. Collectively, the reviewed studies indicate that crocin modulates immune responses at molecular, cellular, and tissue levels through coordinated regulation of cytokine production, inflammatory signaling pathways, oxidative stress mediators, apoptosis, and fibrosis.

According to the reviewed evidence, crocin consistently suppresses major pro-inflammatory cytokines and mediators, including TNF-α, IL-1β, IL-6, IL-8, IL-17, IL-18, IFN-γ, COX-2, iNOS, and ROS generation in both *in vitro* and *in vivo* inflammatory conditions (27, 38, 41, 42, 49, 52, 64, 78, 82, 86, 109, 111). In parallel, crocin frequently enhanced endogenous anti-oxidant defenses, including SOD, CAT, GPx, GSH, FRAP, and total anti-oxidant capacity (74, 78, 91, 96, 100, 101, 115), thereby attenuating oxidative-inflammatory crosstalk that contributes to tissue injury in chronic inflammatory disorders. These findings suggest that suppression of oxidative stress is a major component of crocin-mediated immunoregulation.

Mechanistically, crocin modulated several critical inflammatory signaling pathways implicated in immune dysregulation. Multiple studies demonstrated inhibition of NF-κB signaling (27, 61, 65, 70, 82, 89, 90, 92, 102, 107, 108), TLR4/MyD88 activation (65, 73, 85, 97, 107), NLRP1/NLRP3 inflammasomes, JNK-mediated inflammatory signaling (67, 73, 75, 108), and downstream caspase-dependent apoptotic pathways. Crocin also reduced fibrosis-related signaling through suppression of TGF-β, α-SMA, collagen deposition, and matrix metalloproteinases in pulmonary, hepatic, renal, and musculoskeletal injury models (61, 65, 85, 89, 92, 94). In contrast, crocin activated several pathways including pro-survival PI3K/Akt, neuroprotective CREB/BDNF, anti-oxidant Nrf2, and Bcl-2-associated anti-apoptotic pathways (61, 64, 65, 77-79, 104, 106, 115). Together, these findings indicate that crocin exerts immunomodulatory effects through simultaneous regulation of inflammatory, oxidative, apoptotic, and fibrotic signaling networks rather than through a single molecular target.

An important observation emerging from the reviewed studies is the context-dependent immunoregulatory effect of crocin on T helper (Th)-cell–associated immune responses. In several autoimmune and inflammatory models, crocin suppressed Th1/Th17-associated inflammatory mediators, including IFN-γ, IL-17, IL-1β, IL-6, and TNF-α (38, 41, 49, 102, 111), suggesting attenuation of Th1- and Th17-driven immune activation. Interestingly, in diseases characterized predominantly by Th2-skewed immune responses, including asthma and atopic inflammatory conditions, crocin reduced Th2-associated cytokines such as IL-4, IL-5, and IL-13 (36, 46, 83). These findings suggest that crocin does not simply promote either Th1 or Th2 immunity, but rather functions as a context-dependent immune homeostasis regulator capable of rebalancing dysregulated immune responses according to the prevailing inflammatory microenvironment. Therefore, crocin appears to exert bidirectional immunomodulatory effects that may normalize excessive Th1-, Th2-, or Th17-mediated inflammation depending on disease context.

Despite the promising findings summarized in this review, several limitations remain. Most available evidence originates from animal or *in vitro* studies, whereas clinical investigations remain limited. In addition, substantial heterogeneity exists among studies regarding disease models, treatment duration, dosing regimens, and administration routes, making direct comparisons difficult. The bioavailability and pharmacokinetic properties of crocin also require further investigation to optimize its translational potential. Moreover, although many studies identified modulation of inflammatory signaling pathways, the precise molecular targets and upstream regulators of crocin-mediated immunomodulation remain incompletely understood.

Conclusion

The findings of this review suggest that crocin modulates immune responses primarily through anti-inflammatory and immunoregulatory mechanisms. These properties indicate its potential therapeutic value in immune-mediated disorders, including autoimmune diseases, rheumatoid arthritis, diabetes mellitus (types 1 and 2), and coronary atherosclerosis. Collectively, the evidence presented in this review supports a role for crocin in restoring immune homeostasis by finely tuning pro- and anti-inflammatory signaling pathways rather than inducing broad immunosuppression; however, its effects remain context- and dose-dependent, and potential risks related to immune imbalance or altered host defense cannot be excluded. Comprehensive controlled clinical trials are still required to evaluate further the safety, efficacy, optimal therapeutic range, and potential application of crocin as either monotherapy or adjunctive therapy alongside existing standard treatments for inflammatory and immune-mediated disorders.

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Authors' Contributions

F K and F M were responsible for the study's conceptualization, methodology, and supervision. H A was responsible for writing the original draft and creating the figures. Z A helped prepare the original draft and design the tables. F VS helped write the original draft. H H participated in the critical revision and editing of the article. All authors approved the final version of the manuscript.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Declaration

During the preparation of this manuscript, artificial intelligence-based tools, including DeepSeek and OpenAI (ChatGPT), were used solely for language editing and improvement of clarity and readability. The authors take full responsibility for the content, interpretation, and scientific integrity of the manuscript.

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