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The antidepressant potential of saffron (*Crocus sativus* L.): molecular mechanisms, neurotransmitter modulation, gut-brain axis interactions, and clinical efficacy in major depressive disorder

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Abstract Depression, a prevalent and debilitating mental health disorder, affects approximately 280 million people worldwide, according to the World Health Organization (WHO). It is estimated that 5% of adults, including 4% of men and 6% of women, experience depression, with the prevalence increasing to 5.7% in individuals over 60 years old. Despite the availability of pharmacological treatments, many individuals experience insufficient relief or adverse side effects, highlighting the need for alternative therapies. This review comprehensively examines the current scientific evidence on the mechanisms by which saffron (*Crocus sativus* L.) and its bioactive compounds-crocin, crocetin, and safranal-exert antidepressant effects. Key mechanisms include the modulation of neurotransmitter systems, anti-inflammatory properties, antioxidant activities, and the regulation of neurotrophic factors. Additionally, saffron's impact on epigenetic modulation and gut-brain axis interactions are explored. Clinical studies supporting the efficacy of saffron in alleviating depressive symptoms are discussed, along with considerations for dosage, safety, and future research directions. This review aims to provide a thorough understanding of saffron's potential as a natural antidepressant and its mechanisms of action, contributing to the growing body of literature on alternative treatments for depression.

Keywords Saffron · Major depressive dis order · Antidepressant · Anti-inflammatory · Antioxidant

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Introduction

Depression is a significant cause of disability, impacting over 280 million individuals globally. According to the WHO, approximately 5% of adults, including 4% of men and 6% of women, experience depression, with a higher prevalence of 5.7% in adults over 60 years old. Depression is also about 50% more common in women than men, and more than 10% of pregnant women and those who have recently given birth experience depression. Furthermore, depression is a

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major contributor to suicide, with more than 700,000 people dying by suicide every year, making it the fourth leading cause of death among individuals aged 15–29 years (WHO 2023). Major depressive disorder (MDD) is widely common and is known for its frequent recurrences and severe impairments (Kalmoe et al. 2020). This mental health condition affects people worldwide, regardless of age, race, gender, or socioeconomic status (Otte et al. 2016). MDD is a complex mental health condition with a multifaceted origin. Clinically, it presents with a variety of symptoms including persistent sadness, loss of interest in activities, feelings of hopelessness, thoughts or actions related to suicide, cognitive difficulties, chronic fatigue, feelings of worthlessness, and significant impairment in concentration or decision-making (Miret et al. 2013; Réus et al. 2023). Neuroimaging research has revealed that MDD is primarily characterized by several pathological features. These include reductions in the volume of both cortical and subcortical structures, a decrease in grey matter volume, and significant changes in the density and size of microglial cells (Bora et al. 2012; Zhao et al. 2017). These alterations are linked with irregular neurotransmitter activity and imbalances in gut microbiota (Kunugi 2021).

Individuals with MDD often confront issues such as partial recovery, adverse drug reactions, withdrawal symptoms, and recurrence of the disorder. These challenges pose serious risks to their safety and have substantial negative impacts on society (Levey et al. 2019). Despite significant progress in understanding the pathophysiology of MDD, no single mechanism can fully account for all aspects of this complex disorder. The treatment of MDD primarily relies on the monoaminergic theory, which suggests that the disorder is due to a deficiency of neurotransmitters such as dopamine, noradrenaline, and serotonin in the synaptic cleft (Malhi and Mann 2018). However, only about one-third of individuals with MDD achieve remission after undergoing treatment with a monoaminergic antidepressant (Pallanti et al. 2010). This suggests that other neurobiological mechanisms may be involved in this complex and persistent condition. These mechanisms include genetic and epigenetic factors, elevated glutamate levels, reduced brain-derived neurotrophic factor (BDNF) and its hypermethylation, dysfunction in the hypothalamic–pituitary–adrenal (HPA) axis, oxidative stress, neuroinflammation, and alterations in the microbiota-gut-brain (MGB) axis (Ji et al. 2023).

Changes in gut microbiota can compromise the gut barrier, resulting in increased peripheral inflammation (Carlessi et al. 2021). This inflammation can influence inflammatory pathways that impact brain communication and contribute to stress and MDD. In cases of treatment-resistant depression, the vagus nerve is proposed as a key pathway for neuroinflammation influenced by gut microbiota (Breit et al. 2018). Conventional treatments for depression include medications, electroconvulsive therapy, and psychotherapy. With increasing insights into the molecular pathways of MDD, a range of medications has been introduced, such as Selective Serotonin Reuptake Inhibitors (SSRIs), Tetracyclic Antidepressants (TeCAs), Monoamine Oxidase Inhibitors (MAOIs), and Noradrenergic and Specific Serotonergic Antidepressants (NaSSA). However, these medications can lead to undesired effects such as ineffectiveness, withdrawal symptoms, and side effects. Research suggests that between 30 and 60% of patients with MDD who take medication experience significant side effects, contributing to the growing interest in developing new medications for MDD that are both effective and free from adverse effects (Srikumar et al. 2017). Given these challenges, there is an increasing interest in complementary and alternative medicine, particularly plant-derived compounds, which have shown promising antidepressant effects with fewer side effects.

Currently, herbal remedies are increasingly recognized for their therapeutic potential in managing psychiatric disorders like anxiety and depression. Despite being less potent than conventional drugs, herbal medicines have demonstrated fewer side effects and interactions with other medications. Incorporating herbal remedies alongside traditional antidepressants can mitigate certain side effects such as tremors and agitation, thereby enhancing mental well-being. This combined approach shows promise in addressing depression effectively (Sarris et al. 2011). Several medicinal plants and natural products have been investigated for their potential in managing MDD. *Hypericum perforatum* (St. John's Wort) is one of the most well-studied herbal remedies for depression, with clinical evidence supporting its efficacy comparable to conventional antidepressants but with fewer side effects. The bioactive compounds in St. John's

Wort, particularly hypericin and hyperforin, modulate neurotransmitter levels by inhibiting the reuptake of serotonin, dopamine, and norepinephrine (Ng et al. 2017; Eatemadnia et al. 2019; Kholghi et al. 2022). Another widely researched natural product is *Curcuma longa* (turmeric), which contains curcumin, a polyphenol with anti-inflammatory and neuroprotective properties. Curcumin has been shown to enhance BDNF levels and modulate inflammatory cytokines, potentially contributing to its antidepressant effects (Hurley et al. 2013; Fan et al. 2018, Zhang, Li and Zhang 2020). Additionally, *Rhodiola rosea*, an adaptogenic herb, has been studied for its stress-reducing and mood-enhancing properties. It influences the HPA axis and regulates stress responses, which are often dysregulated in individuals with MDD. Other plant-derived compounds, such as flavonoids found in *Ginkgo biloba* and polyphenols from *Camellia sinensis* (green tea), have also demonstrated neuroprotective and mood-regulating properties (Zhu et al. 2012; Yeh et al. 2015; Esmaeilpour-Bandboni et al. 2021).

Several herbal remedies have been developed into marketed formulations for managing depression. Notable among these is Remotiv, a standardized extract of St. John's Wort that has been approved in various countries as an over-the-counter antidepressant (Yechiam et al. 2019). Curcumin supplements, available in bioavailable formulations such as Longvida® and Theracurmin®, are marketed as adjunct therapies for mood disorders (Small et al. 2018; Cox et al. 2020). Rhodiola-based formulations, such as Rosavin® and Rhodiola Rosea Extract, are also commercially available for stress relief and mental well-being (Dimpfel et al. 2018; Gao et al. 2020). Additionally, green tea polyphenol supplements, particularly those enriched in epigallocatechin gallate (EGCG), are marketed for their cognitive and mood-enhancing benefits (Manshadi Seyed Ali et al. 2021). These products, derived from extensive research on medicinal plants, offer an alternative or complementary approach to conventional antidepressant therapy, providing individuals with more treatment options that may be better tolerated.

The Iridaceae family encompasses a diverse group of flowering plants, consisting of approximately 66 genera and over 2,244 identified species (Christenhusz and Byng 2016). Among them, the *Crocus* genus, which includes around 200 perennial geophyte species, is notable for its medicinal and economic significance. These plants are primarily found in the Mediterranean region, extending into the Irano-Turanian zone (Mohtashami et al. 2021). *Crocus sativus* L., commonly known as saffron crocus, is the most well-studied species within this genus due to its extensive pharmacological properties. Saffron, derived from the dried stigmas of *C. sativus* L., holds immense agricultural and economic value (Cardone et al. 2020). Beyond its use as a culinary spice, saffron has long been incorporated into traditional medicine for treating a variety of ailments. Historically, it has been used to manage conditions such as dysmenorrhea, gastric ulcers, neurological disorders, asthma, and inflammation. Additionally, it has been recognized for its appetite-enhancing and immune-boosting properties. While *C. sativus* L. remains the predominant medicinal species, other members of the *Crocus* genus have also been utilized in traditional healing practices across different cultures (González et al. 2010; Idolo et al. 2010). Given its widespread use in traditional medicine, understanding the pharmacokinetics of saffron's bioactive compounds is crucial for elucidating its therapeutic potential and optimizing its clinical applications.

The absorption, metabolism, and excretion of saffron's bioactive compounds have been extensively examined in pharmacokinetic studies. The key constituents of saffron include crocin, crocetin, picrocrocin, and safranal, all of which exhibit sensitivity to environmental factors such as heat, light, oxygen, and enzymatic degradation. This necessitates careful handling to maintain their bioactivity (Hosseini et al. 2018). Among these, crocin, a water-soluble carotenoid, is largely responsible for saffron's distinctive color (Alavizadeh and Hosseinzadeh 2014). However, oral administration of crocin does not result in its direct absorption into the bloodstream (Xi et al. 2007). Instead, it undergoes enzymatic hydrolysis in the gastrointestinal tract, converting it into crocetin, which then enters systemic circulation (Zhang et al. 2017). Crocetin has been shown to cross the blood–brain barrier through passive diffusion, playing a significant role in saffron's neuroprotective and antidepressant effects (Lautenschläger et al. 2015). In contrast, intravenous administration of crocin results in minimal plasma levels of crocetin, highlighting the digestive system as the main site of its metabolism. Once in circulation, crocetin undergoes further transformation in the liver and intestines, leading to the formation of mono- and di-glucuronide conjugates (Shakya et al. 2020; Xiao et al. 2024). These metabolites are either distributed to target tissues or eliminated through biliary excretion or urine. Studies indicate that the primary route of elimination for crocin and its derivatives is fecal excretion, with minimal renal clearance (Jafarisani et al. 2018).

Saffron, derived from the stigmas of *Crocus sativus* L. (Iridaceae) flowers, is widely recognized as both a spice and a medicinal plant. Its bioactive components, including crocin, crocetin, and safranal, are powerful antioxidants (Jafari et al. 2022). Crocin, a carotenoid that makes up about 10% of saffron, is responsible for its vibrant color. Another significant component, crocetin, is an apocarotenoid dicarboxylic acid that also contributes to the distinctive hue of saffron. Additionally, safranal, an aromatic aldehyde, is the primary component of saffron essential oil and is responsible for its distinctive aroma (Javadi et al. 2013). Saffron may affect levels of neurotransmitters in the brain, including dopamine, norepinephrine, and serotonin. These neurotransmitters play a significant role in depression (Siddiqui et al. 2022). Moreover, saffron and its active components, such as crocin, are effective in treating central nervous system (CNS) disorders. They act as antidepressants, anticonvulsants, memory enhancers, and sedatives (Nassiri-Asl and Hosseinzadeh 2015). Several studies have reported that bioactive compounds in saffron can elevate levels of serotonin, dopamine, and norepinephrine by inhibiting their reabsorption at synapses (Wang et al. 2019; Wauquier et al. 2022). Regular consumption of saffron reduces the activity of the HPA axis by lowering plasma corticosterone levels, which affects cell growth. Previous research has reported that saffron consumption has serotonergic, anti-inflammatory, neuroendocrine, and neuroprotective effects (Rao et al. 2019; Banskota et al. 2021).

Beyond its neuropsychiatric benefits, saffron has also been extensively studied for its therapeutic properties in digestive diseases, particularly those associated with inflammation, oxidative stress, and microbial dysbiosis. Previous studies have demonstrated its efficacy in managing conditions such as gastritis, inflammatory bowel disease (IBD), colitis, and irritable bowel syndrome (IBS) (El-Maraghy et al. 2015; Tadyon Najafabadi et al. 2019; Rezaei et al. 2020; Albalawi et al. 2023). Additionally, emerging evidence suggests that saffron may play a beneficial role in other functional and organic gastrointestinal disorders. In particular, saffron's anti-inflammatory and chemopreventive effects have been explored in relation to colonic adenomas, precancerous lesions that can progress to colorectal cancer (Wang et al. 2020a, b; Bakshi et al. 2022; Pinto et al. 2025). By modulating pro-inflammatory pathways, reducing oxidative stress, and promoting apoptosis, saffron has been proposed as a potential agent in colorectal cancer prevention (Gholipour et al. 2024; Feng et al. 2025). Furthermore, saffron has been investigated for its role in improving post-surgical outcomes in the digestive tract, where complications such as inflammation, oxidative stress, and delayed tissue repair can impact recovery (Arjmand et al. 2021). Studies suggest that saffron's bioactive compounds, including crocin and crocetin, may enhance tissue regeneration and mitigate post-operative inflammatory responses, which are critical factors in reducing complications and improving healing following gastrointestinal surgeries. Given these promising effects, further preclinical and clinical research is warranted to explore saffron's full potential as a complementary therapeutic agent in colonic adenoma prevention and post-surgical recovery (Arjmand et al. 2021).

The objective of this study was to comprehensively assess the potential beneficial effects of saffron in patients with MDD, spanning from its molecular signaling mechanisms to its clinical efficacy. By synthesizing current knowledge and evidence, this review aimed to elucidate how saffron and its bioactive constituents, such as crocin, crocetin, and safranal, may modulate neurotransmitter systems, neuroinflammatory pathways, and neuroendocrine responses implicated in depression. Additionally, this study intends to explore the safety profile and tolerability of saffron as a therapeutic intervention, addressing the need for effective treatments with fewer adverse effects in the management of MDD.

Methods

This narrative review was conducted to explore the potential antidepressant effects of saffron (*Crocus sativus* L.) in major depressive disorder (MDD) by integrating findings on molecular mechanisms, pharmacokinetics, gut-brain axis interactions, and clinical efficacy. A comprehensive literature search was performed using PubMed, Scopus, Web of Science, and Google Scholar, ensuring the inclusion of peer-reviewed articles published in English. No time restrictions were applied, but priority was given to recent publications from the past two decades, with seminal works included when relevant. The search strategy combined keywords and Boolean operators related to saffron (e.g., "saffron," "*Crocus sativus* L.," "crocin," "crocetin," "safranal"), depression (e.g., "major depressive disorder," "mood disorders," "antidepressant"), neurobiological mechanisms (e.g., "serotonin," "dopamine," "BDNF," "oxidative stress," "inflammation," "HPA axis"), gut-brain axis interactions (e.g., "gut microbiota," "short-chain fatty acids," "intestinal permeability"), pharmacokinetics (e.g., "saffron metabolism," "bioavailability," "blood–brain barrier"), and clinical evidence (e.g., "randomized controlled trial," "RCT," "meta-analysis").

Studies were selected based on their relevance to MDD and their contribution to understanding saffron's antidepressant effects through preclinical and clinical investigations. Preclinical studies were included if they examined saffron's effects on neurotransmitter modulation, neuroinflammation, oxidative stress, or gut microbiota in relation to MDD. Clinical trials were considered if they evaluated saffron's efficacy as a standalone treatment or an adjunct therapy. Additionally, pharmacokinetic studies focusing on saffron's metabolism, bioavailability, and gut-brain axis interactions were included, along with review articles and meta-analyses that provided mechanistic insights into saffron's antidepressant potential. Studies were excluded if they lacked experimental data, were unrelated to psychiatric applications of saffron, or did not contribute substantially to understanding saffron's pharmacological effects.

Since this is a narrative review rather than a systematic review or meta-analysis, a formal risk-of-bias assessment was not performed. However, studies were critically evaluated based on their methodological rigor, relevance to the research question, and outcome measures. Factors considered included sample size, use of control groups, and randomization in clinical trials, as well as outcome measures such as Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI), neurotransmitter levels, and inflammatory markers. Findings were synthesized using a qualitative narrative approach, integrating preclinical evidence, molecular insights, and clinical outcomes to provide a comprehensive overview of saffron's potential role in managing depression. Additional references were identified through manual citation tracking of key publications. This review aims to bridge existing knowledge gaps by highlighting saffron's role in depression management, elucidating its mechanisms of action, and outlining potential future directions in both research and clinical applications.

The pathophysiology of major depressive disorder (MDD)

Recent advancements in neuroscience, molecular biology, and bioinformatics have provided deeper insights into the intricate mechanisms underlying major depressive disorder (MDD). This disorder is not attributed to a single cause but results from a complex interplay of multiple biological systems. Key contributing factors include neurotransmitter imbalances, dysregulation of the HPA axis, chronic neuroinflammation, oxidative stress, gut microbiome disturbances, and impaired neurogenesis. These elements do not act independently; rather, they interact dynamically, leading to sustained alterations in neuroplasticity, synaptic connectivity, and neuronal integrity (Cui et al. 2024). Additionally, several molecular pathways, including PI3K/AKT (Li et al. 2017), MAPK/ERK (Behl et al. 2022), NF-κB (Sokołowska et al. 2023), JAK/STAT (Luo et al. 2023), and NLRP3 (Xia et al. 2023) inflammasome signaling, have been implicated in neuronal dysfunction, synaptic degeneration, and neuroimmune activation in MDD. Chronic stress, genetic susceptibility, and environmental influences further exacerbate these dysregulations, contributing to the progression and severity of depressive symptoms (Tian et al. 2022).

Dysregulation of neurotransmitters and receptors in MDD

A hallmark feature of MDD is disrupted neurotransmitter function, particularly in serotonergic (5-HT), dopaminergic (DA), noradrenergic (NE), glutamatergic, and purinergic signaling pathways (Shao and Zhu

2020). While the monoamine hypothesis traditionally suggested that depression arises from a deficiency of key neurotransmitters, recent studies highlight a more complex interplay involving intracellular signaling dysregulation, receptor desensitization, and impaired synaptic remodeling (Pastis et al. 2024).

Serotonin (5-HT) plays a pivotal role in mood regulation, emotional processing, and synaptic plasticity. Deficient serotonin levels have been closely linked to depressive states. SSRIs function by blocking serotonin reuptake via serotonin transporters (SERT), increasing extracellular 5-HT levels in synaptic clefts, and modulating key downstream signaling pathways (Frizzo 2017). Activation of 5-HT1A receptors (5-HT1AR) stimulates PI3K/AKT and MAPK/ERK pathways, promoting neuroprotection and synaptic strengthening. Conversely, 5-HT2B receptors (5-HT2BR) regulate glial cell activity and inflammation, impacting neuroimmune interactions. Chronic treatment with fluoxetine has been shown to activate the ERK1/2/c-Fos axis, enhancing BDNF expression, which supports synaptic plasticity and antidepressant efficacy (Takano et al. 2012; Li et al. 2017). Dopamine is central to reward processing, motivation, and cognitive function, and its dysregulation contributes to anhedonia, reduced motivation, and cognitive impairments in MDD (Fasano et al. 2013; Szczypiński and Gola 2018). Dysfunction within the mesolimbic pathway, particularly involving D2 receptors (D2R) in the ventral tegmental area (VTA) and nucleus accumbens (NAc), has been implicated in depressive symptoms (Shen et al. 2015; Ruan et al. 2025). Chronic stress and overactivation of corticotropin-releasing hormone (CRH) suppress dopaminergic activity by disrupting cAMP/PKA signaling, leading to reduced synaptic plasticity in the prefrontal cortex (PFC) and striatum (Gao et al. 2022; Yan and Rein 2022).

Glutamate, the brain's primary excitatory neurotransmitter, is essential for synaptic communication and neuroplasticity. However, excessive extracellular glutamate can induce excitotoxicity, contributing to neuronal damage and depressive pathology (Chen et al. 2022a; Hao and Plested 2022). Overactivation of N-methyl-D-aspartate receptors (NMDARs) leads to abnormal Ca^{2+} influx, activating MAPK/ERK and calpain cascades, which result in synaptic degradation and mitochondrial dysfunction (Hu et al. 2018). Astrocytes regulate glutamate clearance through glutamate transporters (GLT-1, EAAT2), and deficiencies in these transporters further exacerbate glutamate toxicity and synaptic loss (Soni et al. 2014; Mahmoud et al. 2019).

Norepinephrine (NE), released by the locus coeruleus (LC), regulates neural functions and modulates astrocytic activity (Grimm et al. 2024). Norepinephrine reuptake inhibitors (NRIs) like atomoxetine reduce LPS-induced neuroinflammation (Yssel et al. 2018), while serotonin/norepinephrine NRIs (SNRIs) such as duloxetine, desvenlafaxine, venlafaxine enhance Cx43-mediated astrocytic connectivity (Cui et al. 2024). Venlafaxine boosts FGF-2 and TGF-β1, promoting neuroprotection, while DVS prevents CUMS-induced oligodendrocyte dysfunction, highlighting NE's therapeutic role in MDD (Wang et al. 2014; Zepeda et al. 2016). Extracellular adenosine and ATP modulate neurotransmission and neuroinflammatory responses via purinergic receptors (Zou et al. 2023). Chronic stress conditions lead to elevated ATP release, which activates P2X7 receptors (P2X7R) in microglia and astrocytes, triggering the NLRP3 inflammasome cascade and promoting proinflammatory cytokine release (IL-1β, IL-18), thereby worsening neuroinflammation and depressive symptoms (Wang et al. 2020a, b; Pang et al. 2023).

Dysregulation of the HPA axis and stress-related depression

The HPA axis serves as a critical regulatory system for managing stress responses. In a normal physiological state, corticotropin-releasing hormone (CRH), produced by the hypothalamus, stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH) (Verduijn et al. 2015). ACTH then signals the adrenal glands to synthesize glucocorticoids (GCs), including cortisol, which influences metabolic processes, immune function, and neuronal activity (Kanczkowski et al. 2016). A feedback mechanism ensures that cortisol levels remain within an optimal range, preventing an overactive stress response. However, in MDD, this regulatory system becomes dysregulated, leading to chronic activation of the HPA axis and sustained elevations in cortisol levels (Herbert and Lucassen 2016).

Prolonged exposure to elevated cortisol levels overstimulates glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs), particularly in brain regions responsible for emotion and cognition, such as the hippocampus, prefrontal cortex (PFC), and amygdala (Mora et al. 2012; de Kloet 2022). This overstimulation influences the NR3C1 gene, which encodes GRs, ultimately altering stress responses and synaptic plasticity (Hartmann et al. 2021). Additionally, persistent cortisol elevation interferes with the PI3K/AKT/mTOR signaling cascade, a pathway essential for neuronal survival, synaptic adaptation, and cognitive function (Cai et al. 2015).

Chronic GR activation also triggers epigenetic changes, such as hypermethylation of the FKBP5 gene, which reduces GR sensitivity, reinforcing stress vulnerability (Budziñski et al. 2022). Furthermore, excess cortisol levels promote neuroinflammation via the NF-κB pathway, leading to dysregulated neurogenesis and neural atrophy (Vyas et al. 2016). Evidence suggests that prolonged HPA axis dysfunction contributes to hippocampal shrinkage, exacerbating cognitive impairments and emotional instability in individuals with MDD. Potential therapeutic strategies include GR modulators, FKBP5-targeting drugs, and anti-inflammatory interventions, which may help rebalance the HPA axis and alleviate depressive symptoms (Göver and Slezak 2024).

Additionally, the interaction of thyroid hormones (THs) and estrogen with the HPA axis plays a significant role in the pathophysiology of depression. THs are essential for neuronal development and function within CNS (Zhu et al. 2021). Estrogen affects the serotonin and norepinephrine systems, both of which are involved in the mechanisms underlying depression (Österlund 2010). Leptin, a hormone produced by adipocytes, impacts the HPA axis through its receptors located in different brain regions. This interaction plays a regulatory role in CNS functions and holds potential therapeutic significance for managing depression (Ouakinin et al. 2018).

Neuroinflammation and oxidative stress in depression

A growing body of evidence suggests that neuroinflammation and oxidative stress play fundamental roles in the development and persistence of MDD. These mechanisms contribute to synaptic impairment, neuronal damage, and disturbances in mood regulation (Hassamal 2023). Chronic stress is associated with an increase in proinflammatory cytokines, including interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), which negatively affect neurotransmission and hinder synaptic plasticity. The activation of microglia and astrocytes further amplifies neuroinflammatory responses, leading to persistent neurotoxicity (Hassamal 2023; Zhang et al. 2024). A key driver of neuroinflammation in MDD is the NLRP3 inflammasome, a molecular complex that becomes overactive in response to chronic stress and increased reactive oxygen species (ROS) levels. Once activated in astrocytes and microglia, the NLRP3 inflammasome promotes the release of IL-1β and IL-18, which impair neurogenesis and synaptic signaling. This cascade of inflammatory responses further exacerbates mitochondrial dysfunction, intensifying oxidative damage to neurons (Beckwith et al. 2020; Lin et al. 2021).

BDNF is vital for neuronal growth, survival, and synaptic remodeling. Studies indicate that MDD patients exhibit significantly lower BDNF levels in the hippocampus and PFC, which correlates with cognitive dysfunction and emotional instability (Femenía et al. 2012). Activation of the TrkB receptor by BDNF initiates MAPK/ERK and PI3K/AKT pathways, essential for neuroprotection and synaptic resilience. However, chronic stress and inflammation suppress BDNF-TrkB signaling, leading to neuronal atrophy and diminished synaptic connectivity (Yang et al. 2020; Soman et al. 2025).

Pharmacological approaches such as selective SSRIs and ketamine have been found to increase BDNF expression, inhibit NLRP3 inflammasome activation, and mitigate NF-κB-mediated neuroinflammation. Additionally, therapies targeting oxidative stress, including Nrf2 activators, mitochondrial antioxidants, and inflammasome inhibitors, are being explored as potential neuroprotective interventions for MDD (Casarotto et al. 2021; Miranda et al. 2024).

The role of gut-brain axis disruptions in MDD

The gut-brain axis (GBA) represents a complex communication network that links the CNS, immune system, and gut microbiota (Skonieczna-Żydecka et al. 2018). Growing research suggests that disturbances in gut microbiota composition, known as gut dysbiosis, contribute significantly to MDD pathophysiology (Zheng et al. 2016). Changes in the intestinal microbiota influence immune responses, neurotransmitter synthesis, and metabolic balance, ultimately affecting brain function (Petra et al. 2015). Disruptions in the gut microbiome increase intestinal permeability, allowing bacterial endotoxins such as lipopolysaccharides (LPS) from Gram-negative bacteria to enter the bloodstream (Vincenzo et al. 2024). These molecules activate toll-like receptor 4 (TLR4) on microglia and astrocytes, triggering NF-κB and NLRP3 inflammasome signaling. This inflammatory response compromises blood–brain barrier (BBB) integrity, contributing to neuroinflammation and altered mood regulation (Skrzypczak-Wiercioch and Sałat 2022).

Another critical consequence of gut dysbiosis in MDD is its impact on tryptophan metabolism. Under normal conditions, tryptophan is converted into serotonin (5-HT), a neurotransmitter essential for emotional regulation (Deng et al. 2021). However, dysbiosis shifts tryptophan metabolism toward the kynurenine pathway, leading to the production of quinolinic acid (QUIN)—an NMDA receptor agonist known to induce excitotoxicity and neuronal damage. This metabolic shift results in decreased serotonin levels, further aggravating depressive symptoms (Kearns 2024).

Short-chain fatty acids (SCFAs), such as butyrate, are metabolites produced by beneficial gut bacteria. These compounds support anti-inflammatory processes, neuroprotection, and BBB integrity (Mirzaei et al. 2021). However, in MDD patients, reduced SCFA levels impair mitochondrial function and neuroplasticity, worsening symptoms of depression (Slyepchenko et al. 2016). Emerging probiotic-based interventions, dietary modifications (prebiotics, polyphenols), and fecal microbiota transplantation (FMT) are being investigated as potential therapies for restoring gut homeostasis and improving depressive symptoms (Karakula-Juchnowicz et al. 2019; Khosravi et al. 2020).

Impaired neurogenesis and synaptic plasticity in MDD

Neurogenesis, particularly in the dentate gyrus of the hippocampus, plays a critical role in mood regulation, cognitive flexibility, and emotional stability (Surget and Belzung 2022). Impairments in neuronal growth and synaptic plasticity have been identified as key pathological features of MDD, influenced by chronic stress, neuroinflammation, oxidative stress, and epigenetic modifications (Baptista and Andrade 2018). Neuroimaging and postmortem studies reveal reduced hippocampal volume and lower dendritic spine density in MDD patients, correlating with cognitive and emotional disturbances (Duman and Duman 2015; Malykhin and Coupland 2015). Chronic stress suppresses Wnt/β-catenin signaling and CREB-BDNF pathways, leading to defective neurogenesis and synaptic remodeling (Zhou et al. 2016; Zwamborn et al. 2018). Activation of TrkB receptors by BDNF normally enhances ERK1/2 and PI3K/AKT signaling, which promote neuronal survival and structural plasticity. However, prolonged stress downregulates BDNF expression, further impairing synaptic function (Yoshii and Constantine-Paton 2010).

Epigenetic alterations, such as methylation of BDNF gene promoters and histone modifications, contribute to impaired neurogenesis (Ikegame et al. 2013). Astrocytes and microglia regulate neuronal function by releasing growth factors (BDNF, GDNF, VEGF) and inflammatory cytokines (Cabezas et al. 2016). Activation of the NLRP3 inflammasome and NF-κB in astrocytes reduces BDNF production, worsening depressive symptoms (Caviedes et al. 2017; Yang et al. 2022). Antidepressants such as SSRIs, ketamine, and electroconvulsive therapy (ECT) stimulate hippocampal neurogenesis by enhancing BDNF-TrkB signaling and improving synaptic connectivity (Rantamäki 2019). Novel therapeutic strategies, including Wnt/β-catenin modulation, HDAC inhibitors, and neurotrophic factor-based interventions, hold promise in reversing synaptic deficits and restoring cognitive function in MDD (Vidal et al. 2011).

Genetic influences on MDD pathophysiology

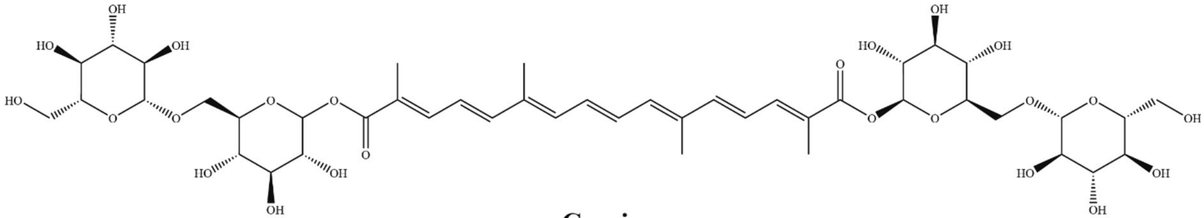
Genetic factors play a crucial role in the onset of MDD. This is supported by data from family, twin, and adoption studies, as well as epidemiological research (Lohoff 2010). The heritability of MDD is particularly significant in women, which aligns with the higher rates of depression observed in females (Silveira et al. 2023). Various genes are associated with depression, though only a limited number of genetic polymorphisms are strongly linked to MDD. Notable examples are apolipoprotein E (APOE), guanine nucleotidebinding protein (GNB3), methylenetetrahydrofolate reductase (MTHFR), dopamine transporter (SLC6A3), serotonin transporter (SLC6A4), and dopamine receptor gene (DRD4) (Lohoff 2010). Research has disclosed APOE ε4 is linked to diminished brain structure and cognitive abilities in individuals with depression, whereas APOE ε2 is seen as a protective factor. Nonetheless, some studies have not established a significant connection between APOE and depression (Surtees et al. 2009; Feng et al. 2015). The DRD4 gene is more highly expressed in people with MDD, as well as in postmortem samples from depressed individuals (Opmeer et al. 2010). Those with the SLC6A4 gene demonstrate increased amygdala activity and a stronger reaction to stress. Additionally, genes like GNB3, SLC6A3, and SLC6A4 are targets for therapeutic treatments, emphasizing the genetic influence on the pathophysiology of depression (Gonda et al. 2019). A recent meta-analysis highlighted 44 independent loci linked to the disorder. These results suggest anatomical variations in the anterior cingulate cortex and prefrontal cortex, regions already known to exhibit structural and functional differences between MDD patients and control groups. The research also identified strong associations between depression and specific gene sets that encode proteins targeted by antidepressant medications, which may help explain the therapeutic effectiveness of these treatments (Wray et al. 2018).

Environmental stressors in MDD pathophysiology

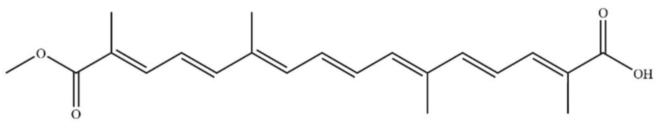
Environmental stress and adverse life events play a crucial role in the onset and progression of MDD. Studies consistently demonstrate a prevalence of highly stressful life events preceding the emergence of depression, including the loss of a spouse, marital separation, unemployment, social isolation, and experiences of childhood abuse. These stressors not only initiate the onset of depressive episodes but also hinder recovery efforts and heighten the risk of recurrence (Lichtenberg and Belmaker, 2010). Stress and depression involve overlapping mediators and neural circuits. Reduced exposure to stress may provide a protective effect against depression, suggesting that dysregulation of the stress response system could be a contributing factor to the development of depression (Gold 2015). Animal research corroborates this by demonstrating that stress triggers alterations in the structure and function of brain areas like the prefrontal cortex, amygdala, hippocampus, and nucleus accumbens, all of which are implicated in the development of depression (McEwen et al. 2016). Studies involving identical twins underscore the influence of environmental stressors on the development of depression. These studies reveal that twins who develop depression often encounter more severe life events, such as the end of a romantic relationship, divorce, or traumatic brain injury, compared to their unaffected siblings (Schnittker 2010; Kendler et al. 2011). The severity and characteristics of depressive episodes can be significantly influenced by the frequency, duration, type, and persistence of stressors (Su et al. 2024). While both short-term and prolonged stressful life events can initiate and sustain major depression, positive experiences such as strong personal relationships, marital satisfaction, academic and professional achievements, and economic security have been shown to enhance treatment outcomes and potentially lower the risk of developing depression (Smorti et al. 2019).

Bioactive compounds and chemical composition of Saffron

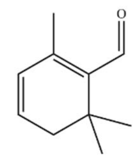
Crocus sativus L. (Saffron) is widely used for coloring and flavoring food globally and serves as a therapeutic agent for various medical conditions. Saffron, derived from the dried stigmas of *C. sativus* L. flowers, is a renowned spice with notable antidepressant properties. Saffron acts as a protective agent against chromosomal damage, modulates lipid peroxidation, and has antiseizure properties that help reduce blood pressure. Chemical analyses of saffron extract have identified approximately 150 distinct compounds, with crocin, crocetin, safranal, and picrocrocin being the key bioactive constituents. Saffron typically contains about 30% crocin, 5%–15% picrocrocin, and up to 2.5% volatile compounds, including safranal. The predominant components of saffron extract are carotenoids, particularly crocin, and crocetin (Fig. 1). The coloring agents in saffron are crocins, unique water-soluble carotenoids (cis- and trans-glucosyl esters of crocetin). Monoterpene aldehydes like picrocrocin and its deglycosylated form, safranal (dehydro-β-cyclocitral), contribute to saffron's bitter taste and distinctive aroma, respectively.



Crocin



Crocetin



Safranal

Fig. 1 The chemical structure of the main bioactive constituents of saffron

Crocin ($C_{44}H_{64}O_{24}$), the compound that gives saffron its distinctive red hue, is a hydrophilic carotenoid with a molecular weight of 976.96. Its structure can vary based on the glycosyl esters, like glucose, gentiobiose, and triglucose, attached to its side chains. The most prevalent form, crocin 1 (or α-crocin), is formed from the disaccharide gentiobiose and crocetin (Bian et al. 2020). Picrocrocin ($C_{16}H_{26}O_7$), a crystalline terpene-glucoside with a molecular weight of 330.37, imparts the bitter flavor to saffron. It acts as a precursor to saffron's aromatic elements, transforming into hydroxy-safranal through enzymatic activity and dehydration during storage and processing (Samarghandian and Borji 2014). Safranal, the primary constituent of saffron's volatile oil, is responsible for its distinctive fragrance. It is derived from picrocrocin through de-glycosylation and dehydration processes, with its levels influenced by storage conditions. The highest concentration of safranal is preserved for up to one year following harvest (Maggi et al. 2010).

Saffron's neuroprotective mechanisms in neurological disorders

Crocus sativus L. (saffron), particularly through its primary bioactive compounds such as crocin, crocetin, and safranal, exhibits significant neuroprotective properties. These protective mechanisms are primarily mediated through anti-inflammatory, antioxidant, and anti-apoptotic effects (Fig. 2). These compounds are widely studied for their therapeutic potential against various neurological disorders.

One of the critical neuroprotective mechanisms of saffron is its anti-inflammatory effects. Chronic inflammation is a hallmark of many neurodegenerative diseases, and saffron compounds have been shown to mitigate this inflammation. Specifically, they inhibit the expression of pro-inflammatory cytokines, such as TNF-α and interleukins (IL-1β, IL-6), which are commonly elevated in conditions like Alzheimer's disease and Parkinson's disease (Sadoughi 2019). Dong et al. (2020) demonstrated that saffron's anti-inflammatory properties significantly reduced the expression of these cytokines in a Parkinson's disease model using C57BL/6 mice (Dong et al. 2020). Additionally, Banskota et al. (2021) observed similar effects in a rat model of dextran sulfate sodium (DSS)-induced colitis, indicating that saffron's anti-inflammatory actions could be beneficial across different inflammatory conditions (Banskota et al. 2021). In addition, crocin exhibits strong anti-inflammatory effects by lowering levels of inflammatory markers such as TNF-α and IL-1β. It acts on the NF-κB signaling pathway to reduce the

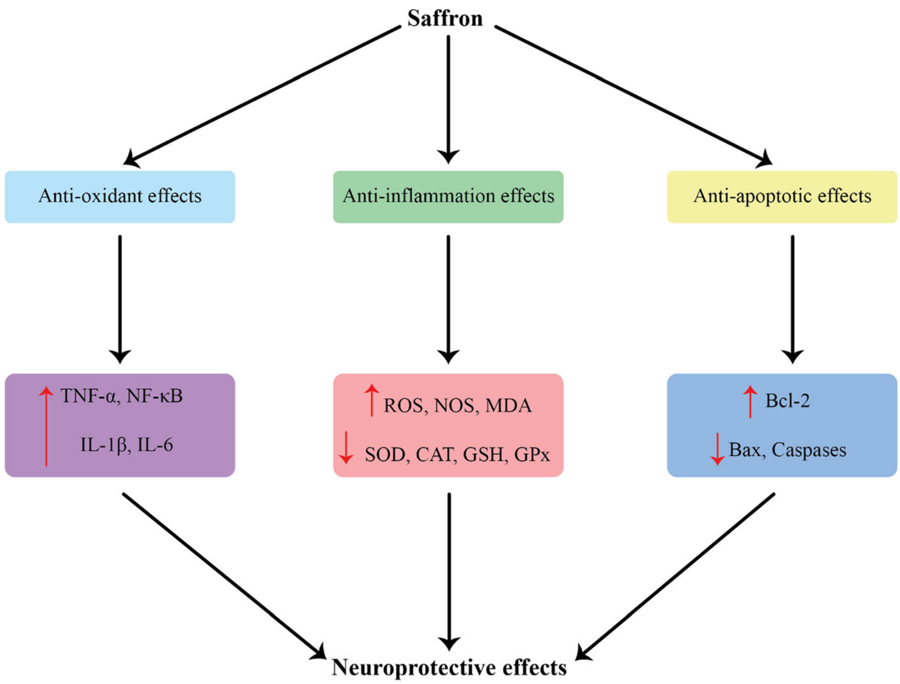


Fig. 2 The mechanisms of neuroprotective effects of saffron

release of pro-inflammatory cytokines, thereby alleviating inflammation associated with neurodegenerative processes (Heidari et al. 2017).

In addition to its anti-inflammatory properties, saffron exhibits robust antioxidant effects, which are crucial for protecting neurons from oxidative stress. Oxidative stress, characterized by an imbalance between the production of ROS and the body's ability to detoxify these harmful compounds, is a major contributor to neuronal damage (Cerdá-Bernad et al. 2022). Saffron compounds, particularly crocin, have been shown to reduce levels of ROS and lipid peroxidation products such as malondialdehyde (MDA). Mousavi et al. (2010) demonstrated that saffron significantly lowered ROS levels in neuronal cells, providing a protective effect against oxidative damage saffron significantly lowered ROS levels in neuronal cells, providing a protective effect against oxidative damage. Furthermore, Huang and Jia (2021) found that crocin reduced MDA and nitric oxide (NO) levels in models of hypoxic-ischemic encephalopathy, highlighting its potential to mitigate oxidative stress-related neuronal injury (Huang and Jia 2021). Moreover, saffron compounds enhance the activity of endogenous antioxidant enzymes, which play a vital role in neutralizing oxidative stress. These enzymes include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Sun et al. (2020) demonstrated that in an MK-801-induced schizophrenia rat model, crocin administration markedly reduced malondialdehyde (MDA) levels (from ~ 5.5 nmol/mg in the MK-801 group to ~ 3.0 nmol/mg and ~ 1.8 nmol/mg in the 25 mg/kg and 50 mg/kg crocin-treated groups, respectively). Additionally, T-SOD activity was significantly restored, increasing from ~ 60 U/mg in the MK-801 group to ~ 120 U/mg and ~ 160 U/mg with 25 mg/kg and 50 mg/kg crocin, respectively. Similarly, CAT and GPx activities were significantly enhanced, with CAT activity rising from ~ 1.0 U/mg in the MK-801 group to ~ 1.6 U/mg and ~ 2.2 U/mg with crocin treatment, while GPx activity improved from ~ 1.5 U/mg to ~ 2.5 U/mg and ~ 3.5 U/mg in the respective treatment groups. These findings suggest that saffron, particularly crocin, effectively mitigates oxidative stress by restoring antioxidant enzyme activity and reducing lipid peroxidation, highlighting its potential as a neuroprotective agent in oxidative stress-related disorders (Sun et al. 2020). Similarly, Rao et al. (2019) highlighted the antioxidant benefits of crocin in Parkinson's disease models, where it restored dopamine levels and reduced oxidative stress markers, thereby protecting neuronal integrity and function (Rao et al. 2019). Crocin also enhances the glutathione pathway by elevating levels of reduced glutathione (GSH) while reducing oxidized glutathione (GSSG), thereby restoring antioxidant defense mechanisms. This equilibrium plays a crucial role in safeguarding neural cells from potential damage and promoting their survival (Ochiai et al. 2004; Mozaffari et al. 2019). Furthermore, crocin supports the function of mitochondria, crucial for the survival of neural cells, by preserving mitochondrial membrane potential, fostering the generation of new mitochondria, and decreasing oxidative damage to mitochondrial DNA (Zhang et al. 2015).

The anti-apoptotic effects of saffron compounds further contribute to their neuroprotective potential. Apoptosis, or programmed cell death, is a significant factor in the progression of neurodegenerative diseases. Saffron compounds, such as crocin and safranal, inhibit the expression of pro-apoptotic factors like caspases and Bax while promoting anti-apoptotic factors such as Bcl-2 (Asadi et al. 2015). Abdel-Rahman et al. demonstrated that saffron's anti-apoptotic responses involved regulating apoptotic proteins in models of ischemic brain injury, thereby reducing cell death (Abdel-Rahman et al. 2020). Additionally, saffron compounds help maintain mitochondrial integrity and function, which is crucial for cell survival. Crocin also plays a role in preventing apoptosis, which is a significant factor in neurodegenerative diseases, by influencing both intrinsic and extrinsic pathways of apoptosis. It decreases the levels of pro-apoptotic proteins such as Bax, enhances the levels of anti-apoptotic proteins such as Bcl-2, and reduces the activity of caspase-3. This action helps protect neural cells from undergoing programmed cell death (Asadi et al. 2015; Shafahi et al. 2018). Thus, saffron exerts its neuroprotective effects through a combination of anti-inflammatory, antioxidant, and anti-apoptotic mechanisms. These effects are mediated by its bioactive compounds, which regulate key molecular pathways involved in neuroinflammation, oxidative stress, and cell survival. The therapeutic potential of saffron in neurological disorders is supported by numerous studies, indicating its promise as a natural intervention for neuroprotection. While saffron's neuroprotective effects are well-documented, recent research highlights its ability to modulate gut microbiota, further reinforcing its role in the gut-brain axis and depression management. The following section explores how saffron influences gut microbiota composition, SCFA production, and gut-derived neurotransmitters.

Saffron's role in modulating the gut-brain axis

The gut-brain axis plays a crucial role in depression, as gut dysbiosis has been linked to neuroinflammation and neurotransmitter imbalances. Given this emerging understanding, natural compounds like saffron (*Crocus sativus* L.) have gained attention for their ability to restore microbial homeostasis. Preclinical and clinical studies suggest that saffron and its bioactive compounds enhance microbial diversity, promote SCFA production, and improve gut barrier integrity, which may contribute to its antidepressant properties (Table 1).

Saffron's impact on gut microbiota composition

Several studies have demonstrated that saffron modulates gut microbiota composition, which may contribute to its neuroprotective effects. Peng et al. (2023) found that saffron petal extract (200–400 mg/kg/day) in a DSS-induced colitis model increased the abundance of beneficial bacterial species such as *Bacteroides acidifaciens*, *Bacteroides vulgatus*, *Lactobacillus murinus*, and *Lactobacillus gasseri*, which are known to enhance gut integrity and reduce inflammation. Similarly, Xiao et al. (2020) reported that crocin-I supplementation (40 mg/kg) in chronic stress mice led to an increase in *Firmicutes*, *Lactobacillus spp*., and *Bacteroides spp*., while reducing the pro-inflammatory bacterial groups *Proteobacteria* and *Bacteroidetes*, effectively restoring microbial balance and improving mood-related behaviors.

The transformation of crocin-1 into crocetin via gut microbiota metabolism was confirmed by García et al. (2024) through in vitro human fecal fermentation studies, highlighting the role of gut microbiota in the bioavailability and potential neuroprotective effects of saffron. Additionally, Chen et al. (2022a, b) demonstrated that a flavonoid extract from saffron floral bio-residues (1.5 g/kg/day) in hyperuricemic rats corrected gut microbiota dysbiosis and restored lipid and amino acid metabolism without causing kidney

Table 1 The antidepressant potential of saffron (*crocus sativus l.*): from molecular mechanisms to gut microbiota modulation and clinical evidence

Study	Study design	Saffron dosage	Duration	Key findings	Health outcomes
Peng et al. (2023)	Animal model (DSS-induced colitis in mice)	Saffron petal extract (200 and 400 mg/kg/day)	7 days	Increased *Bacteroides acidifaciens*, *Bacteroides vulgatus*, *Lactobacillus murinus*, and *Lactobacillus gasseri*	Alleviated colitis by reducing macrophage activation and modulating gut microbiota
García et al. (2024)	In vitro (human fecal fermentation)	Crocin-1 and Crocetin (10 µM)	0–240 h	Transformation of crocin-1 into crocetin via gut microbiota metabolism; altered SCFA production	Suggested potential involvement of gut microbiota in neuroprotective effects
Chen et al. (2022a, b)	Animal model (hyperuricemic rats)	Flavonoid extract from saffron floral bio-residues (1.5 g/kg/day)	21 days	Modulated gut microbiota dysbiosis and restored lipid and amino acid metabolism	Lowered uric acid levels without kidney damage
Banskota et al. (2021)	Animal model (DSS-induced colitis in mice)	Saffron extract (10 and 20 mg/kg)	11 days	Increased short-chain fatty acids (SCFAs); distinct gut microbiome clusters	Reduced colitis severity, suppressed pro-inflammatory cytokines (TNF-α, IL-1β, IL-6)
Singh et al. (2023)	Animal model (DSS-induced colitis in mice)	Saffron (20 mg/kg)	10 days	Maintained *Firmicutes/Bacteroides* ratio, counteracted pro-inflammatory bacteria	Reduced colitis symptoms and gut inflammation
Agarwal, Kolba et al. (2022)	Animal model (Gallus gallus model)	Saffron flower water extract (1–10%)	21 days	Reduced *Lactobacillus* and *Clostridium* sp., increased Paneth cell number, Mucin 2 expression	Negative impact on gut barrier function, mineral absorption, and microbiota
Feng, Li et al. (2022)	Animal model (DSS-induced colitis in mice)	Crocetin (0–40 mg/kg/day)	21 days	Increased *Akkermansia*, *Mediterraneibacter*; reduced *Muribaculaceae*, *Dubosiella*, *Parasutterella*, *Allobaculum*	Prolonged colitis recovery by altering microbiome and increasing gut permeability
Baldi, Pagliai et al. (2024)	Clinical trial (nAMD patients)	supplement containing saffron (20 mg), lutein (10 mg), zeaxanthin (2 mg), vitamin C (80 mg), vitamin E (12 mg), and zinc (10 mg)	6 months	Increased total SCFA levels, improved gut microbiota diversity	Enhanced visual acuity in nAMD patients
Xie et al. (2019)	Animal model (CORT-treated mice)	Crocin-I (0–40 mg/kg)	21 days	Increased *Bacteroidetes*, decreased Firmicutes	Restored gut microbiota balance and lipid metabolism
Lin et al. (2021)	Animal model (chronic stress mice)	Crocetin (20–80 mg/kg)	42 days	Gut microbiome changes correlated with neuroprotection	Alleviated depressive behaviors and hippocampus injury

Table 1 continued

Study	Study design	Saffron dosage	Duration	Key findings	Health outcomes
Han et al. (2022)	Animal model (LDLR knockout mice)	Crocin (20–40 mg/kg)	56 days	Increased intestinal tight junction proteins, improved microbiome composition	Reduced inflammation and oxidative stress in atherosclerosis
Xiao et al. (2020)	Animal model (chronic stress mice)	Crocin-I (40 mg/kg)	42 days	Increased *Firmicutes*, *Lactobacillus* spp., *Bacteroides* spp.; reduced *Proteobacteria*, *Bacteroidetes*	Alleviated depression-like behavior via gut-brain axis modulation
Xie, Zhang et al. (2022)	Animal model (HFD-induced obese mice)	Crocin-I (20 mg/kg)	10 weeks	Increased SCFAs, decreased *Proteobacteria*, improved intestinal barrier function	Reduced obesity-related inflammation and gut dysbiosis
Chen et al. (2024)	Animal model (chronic stress mice)	Saffron (mg/kg) + Probiotic WHH2078 (5×10^8 CFU/mL)	4 weeks	Increased *Ligilactobacillus*, *Candidatus Arthromitus*, *Erysipelatoclostridium*	Improved depressive behaviors and gut microbial diversity
Begas et al. (2019)	Clinical trial (healthy volunteers)	Saffron infusion (300 mg in 150 mL hot water)	6 days	Reduced CYP1A2 enzyme activity, potential microbiota interactions	Possible implications for drug metabolism
Pontifex et al. (2022)	Animal model (low-grade inflammation mice)	Saffron extract (22 mg/day human equivalent)	56 days	Increased *Akkermansia*, *Muribaculaceae*, *Christensenellaceae*, *Alloprevotella*	Improved anxiety-related behavior via gut-brain axis
Li et al. (2021a, b)	Animal model (Zucker diabetic fatty rats)	LLKL (herbal formula with saffron, 0–4.68 g/kg/day)	42 days	Increased gut microbiota diversity, reduced LPS, TNF-α, IL-6	Improved blood sugar control and gut-liver axis function

damage, further emphasizing saffron's systemic metabolic benefits.

Saffron's influence on gut-derived metabolites and SCFAs

SCFAs such as butyrate, acetate, and propionate play a crucial role in gut-brain communication by modulating inflammation, maintaining blood–brain barrier integrity, and supporting neuronal function (Majumdar et al. 2023). Saffron supplementation has been shown to increase SCFA production, which may contribute to its antidepressant effects. Banskota et al. (2021) reported that saffron extract (10–20 mg/kg) in DSS-induced colitis models significantly increased SCFA levels while suppressing pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), suggesting its potential role in reducing neuroinflammation linked to gut dysbiosis. Similarly, Xie et al. (2022) demonstrated that crocin-I administration (20 mg/kg) in obese mice not only increased SCFA production but also improved intestinal barrier function, further supporting its gut-mediated neuroprotective effects. In a human clinical trial, Baldi et al. (2024) found that a saffron-containing supplement (20 mg) combined with lutein, zeaxanthin, vitamin C, vitamin E, and zinc over six months increased total SCFA levels and improved gut microbiota diversity, reinforcing saffron's role in microbiome modulation with potential antidepressant benefits.

Gut barrier integrity and anti-inflammatory effects of saffron

A disrupted gut barrier leads to increased intestinal permeability, allowing LPS and pro-inflammatory cytokines to enter circulation, thereby triggering neuroinflammation and depressive symptoms. Saffron has been shown to enhance gut barrier integrity by upregulating intestinal tight junction proteins and reducing gut-derived inflammation. Han et al. (2022) demonstrated that crocin (20–40 mg/kg) increased intestinal tight junction proteins, leading to improved microbiome composition and reduced oxidative stress in an atherosclerosis model. Additionally, Pontifex et al. (2022) found that saffron extract (22 mg/day human equivalent) in low-grade inflammation mouse models increased beneficial bacteria (*Akkermansia*, *Muribaculaceae*, *Christensenellaceae*, and *Alloprevotella*), correlating with improved anxiety-related behaviors via the gut-brain axis. Furthermore, Chen et al. (2024) investigated the combined effects of saffron and a probiotic strain (WHH2078, 5×10^8 CFU/mL) in chronic stress mice and found that this combination significantly increased beneficial bacteria such as *Ligilactobacillus*, *Candidatus Arthromitus*, and *Erysipelatoclostridium*, while improving depressive behaviors and gut microbial diversity, suggesting a synergistic effect between saffron and probiotics in modulating gut-brain interactions.

Saffron's effect on tryptophan metabolism and neurotransmitter regulation

Tryptophan metabolism plays a pivotal role in mood regulation, as its conversion into serotonin (5-HT) or kynurenine determines its antidepressant or neurotoxic potential. Gut microbiota influences this metabolic pathway, and saffron appears to modulate it favorably. Lin et al. (2021) demonstrated that crocetin (20–80 mg/kg) in chronic stress mice altered gut microbiome composition, correlating with improved neuroprotection and hippocampal function. This suggests that saffron may shift tryptophan metabolism towards serotonin production while reducing neurotoxic kynurenine derivatives, thereby alleviating depressive symptoms. Additionally, Xie et al. (2019) reported that crocin-I administration (0–40 mg/kg) in CORT-treated mice increased Bacteroidetes while decreasing Firmicutes, restoring gut microbiota balance and improving lipid metabolism, further supporting saffron's role in gut-derived neurotransmitter regulation.

Hence, the evidence from both preclinical and clinical studies suggests that saffron exerts antidepressant effects through multiple gut-brain axis mechanisms, including microbiota modulation, SCFA production, gut barrier reinforcement, anti-inflammatory effects, and tryptophan metabolism regulation. Given its potential to restore microbial diversity and enhance gut-derived neuroprotection, saffron represents a promising natural intervention for MDD.

The impacts of Saffron on depression: preclinical and clinical evidence

This section of the manuscript delves into the effects of saffron (*Crocus sativus* L.) on depression, drawing insights from both preclinical studies using animal models with induced depressive-like behaviors and clinical trials involving patients diagnosed with MDD. Preclinical studies are crucial as they employ various experimental paradigms to induce depressive-like behaviors in animals, simulating aspects of depression such as anhedonia, despair, and social withdrawal. These studies provide valuable insights into the potential mechanisms and therapeutic effects of saffron in mitigating these behaviors. Clinical trials, on the other hand, involve human subjects diagnosed with MDD, where saffron's therapeutic potential is evaluated through rigorous methodologies and standardized assessment tools for depression. These trials assess saffron's efficacy in alleviating depressive symptoms, improving mood, and enhancing overall quality of life in patients. Clinical trials reviewed here assess saffron's effectiveness as a standalone treatment or adjunct therapy compared to placebo or conventional antidepressants. They provide valuable evidence regarding saffron's safety, tolerability, and potential side effects in human populations. Moreover, these trials explore the optimal dosage and duration of saffron treatment necessary to achieve therapeutic benefits in patients with MDD. Table 2 summarizes the key preclinical studies and clinical trials discussed in this section, highlighting the diverse methodologies, outcomes, and implications of saffron in depression research. By synthesizing findings from both preclinical and clinical studies, this section aims to provide a comprehensive overview of saffron's role in depression management, highlighting its promise as a natural therapeutic agent with multifaceted effects on neurobiology and mood regulation (Fig. 3).

Table 2 Preclinical studies on the antidepressant effects of saffron and its bioactive compounds

Active compound	Experimental design and methodologies	Dose and duration	Key findings	References
Saffron extract (Safr'Inside™)	Ex vivo clinical approach with human neurons	0–300 mg/kg of a saffron extract, 1 time	Saffron metabolites protected human neurons from oxidative stress-induced neurotoxicity, enhanced dopamine and serotonin release, and modulated serotonin transporter expression and metabolism	(Wauquier et al. 2022)
	Unpredictable chronic mild stress in mice	0–600 600 mg/Kg/day, 21 days	Safr'Inside™ reduced depressive-like behavior in FST. Modulated serotonergic and dopaminergic neurotransmission. Potential similar targets to conventional antidepressants	(Monchaux De Oliveira et al. 2021a)
	Acute restraint stress (ARS) in mice	0–600 mg/Kg, 1 time	Safr'Inside™ attenuated ARS-induced depressive-like behavior. Modulated monoamine dysregulation, and reduced kynurenine-related neurotoxicity	(Monchaux De Oliveira et al. 2021b)
Affron® (saffron extract)	Social isolation in mice	0–200 mg/Kg, 1 time	Affron® (saffron extract) improved anxious/depressive behaviors. Enhanced sucrose preference and escape responses	(Orio et al. 2020)
Aqueous saffron extract	Chronic restraint stress in rats	0–160 mg/kg/day, 21 days	Aqueous saffron extract reduced immobility time in FST. Increased protein levels of BDNF, CREB, p-CREB in rat hippocampus	(Ghasemi et al. 2015)
Saffron essential oil (SEO)	Chronic unpredictable mild stress in mice	Inhalation of diluted SEO (2%, 4%, and 6% SEO), 21 days	SEO improved depressive-like behaviors. Enhanced 5-HT, DA, BDNF levels. Regulated MAPK-CREB1-BDNF signaling pathway	(Chen et al. 2023)
Crocus sativus gold nanoparticles (CS-AuNPs)	Depression model in mice	0–150 mg/kg, duration was not mentioned	CS-AuNPs reduced proinflammatory cytokines, inhibited NF-κB activation, enhanced antioxidant activities, and potential safer antidepressant	(Li et al. 2024)
Crocetin	Chronic restraint stress in rats	0–60 mg/kg/day, 21 days	Crocetin ameliorated depressive-like effects induced by chronic stress. Reduced immobility time in forced swim test (FST) and increased locomotor activity. Reversed oxidative damage markers (MDA, GSH) and restored antioxidant enzyme activities in the brain	(Farkhondeh et al. 2018)
	Chronic restraint stress in mice	0–80 mg/kg/day, 28 days	Crocetin attenuated depressive-like behaviors. Reduced MKP-1, proBDNF, increased DA, CREB levels. Neuroprotective effects in hippocampus and modulation of intestinal microbiota	(Lin et al. 2021)
	Chronic restraint stress in mice	0–80 mg/kg/days, 2 days	Crocetin exhibited rapid antidepressant effects within hours. Reduced inflammatory factors, and restored PI3K/AKT signaling. Long-lasting effects up to 2 days	(Lin et al. 2024)
Crocin	Chronic unpredictable mild stress in mice	0–40 mg/kg/day, not mentioned duration	Crocin-1 improved depressant-like behaviors in CUMS-induced mice. Increased neurotransmitter levels (DA, 5-HT) and brain-derived neurotrophic factor (BDNF) modulated MKP-1/CREB/BDNF pathway	(Wang et al. 2019)
	Unpredictable chronic mild stress in rats	0–30 mg/kg/day, 28 days	Crocin improved UCMS-induced anxiety and depression. Reduced oxidative stress and inflammation markers, increased BDNF levels	(Abbaszade-Cheragheali et al. 2022)
Crocin and Crocetin	Unpredictable chronic mild stress in rats	Crocin (0–30 mg/kg/day) and Crocetin (0–10 mg/kg/day), 21 days	Crocin and Crocetin attenuated depression and anxiety. Increased serotonin and decreased corticosterone. Modulated CREB, ERK, BDNF pathways in hippocampus. Interacted with SERT and NR2B subunit of NMDA receptor	(Mohammadi et al. 2023)

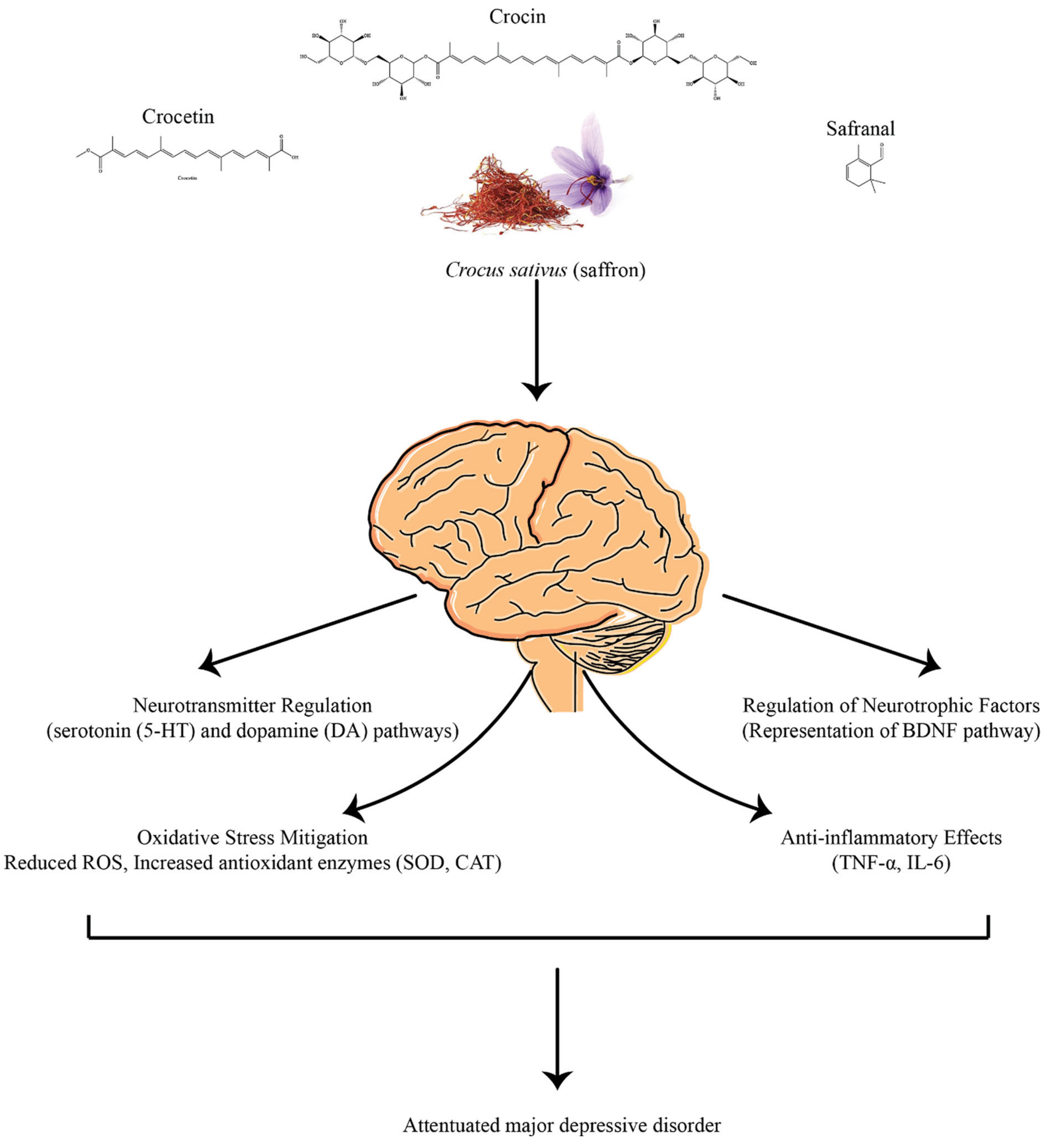


Fig. 3 The role of saffron and its bioactive compounds in major depressive disorder

Preclinical insights into Saffron's antidepressant effects

This section explores preclinical studies investigating the antidepressant effects of saffron and its bioactive compounds, crocetin, crocin, and safranal, in various animal models of depression. Augmented oxidative stress was found to play a crucial role in susceptibility to depression, with antidepressant medications shown to reduce this stress in patients. Saffron is recognized for its anti-inflammatory and antioxidant properties, and its positive impact on depression, potentially through SSRI-like mechanisms. However, the precise molecular pathways through which saffron exerts these effects were unclear. An innovative ex vivo clinical approach demonstrated for the first time that circulating human metabolites produced after saffron intake (Safr'Inside^{TM}) protected human neurons from oxidative-stress-induced neurotoxicity by preserving cell viability and increasing BNDF production. These metabolites significantly stimulated the release of both dopamine and serotonin. Furthermore, saffron metabolites protected serotonergic function by inhibiting the expression of the SERT and down-regulating serotonin metabolism. These findings provided new biochemical insights into how saffron supports neuronal health and function in humans, particularly in relation to oxidative stress associated with depression (Wauquier et al. 2022). A preclinical investigation aimed to evaluate saffron extract's effects on mood in mice and uncover its underlying mechanisms, focusing on monoaminergic neurotransmission, crucial for mood regulation. The study utilized Safr'Inside^{TM} at a dosage of 6.5 mg/kg orally in naïve mice. Results indicated that saffron extract reduced depressive-like behaviors in the forced swim test, accompanied by changes in serotonergic and dopaminergic pathways. These findings suggest that saffron extract may target similar pathways as conventional antidepressants, offering promising insights into its therapeutic potential for mood disorders (Monchaux De Oliveira et al. 2021a). The anti-depressant effects of saffron were observed in mice subjected to acute restraint stress (ARS). Administration of Safr'Inside^{TM} (6.25 mg/kg/day) before the onset of stress significantly mitigated ARS-induced depressive-like behavior in the forced swim test. Furthermore, Safr'Inside^{TM} reversed stress-induced dysregulations in monoamine levels and modulated enzymes in the kynurenine pathway, potentially reducing kynurenine-related neurotoxicity. These findings highlight saffron's ability to prevent the development of stress-induced depressive symptoms and provide insights into its mechanisms of action, supporting its therapeutic potential in depression management (Monchaux De Oliveira et al. 2021b).

The anti-depressant effects of saffron essential oil (SEO) were investigated in mice subjected to chronic unpredictable mild stress (CUMS). SEO, primarily through its active compounds, enhanced serotonin (5-HT), dopamine (DA), brain-derived neurotrophic factor (BDNF), and γ-aminobutyric acid (GABA) levels in serum. Behavior tests indicated improved depressive-like behaviors, and histopathological assessments showed SEO's neuroprotective effects in the hippocampus. Increased expressions of Raf1, MEK1, P-ERK1/2/ERK1/2, P-CREB1/CREB1, BDNF, and P-Trk B/Trk B suggested the involvement of the MAPK-CREB1-BDNF signaling pathway in SEO's antidepressant mechanism. The study concluded that SEO effectively alleviates depression symptoms induced by CUMS and mitigates hippocampal neuronal damage, with optimal efficacy observed at 4% SEO concentration (Chen et al. 2023). A recent study developed saffron gold nanoparticles (CS-AuNPs) using a non-toxic and environmentally friendly method, enhancing the bioavailability and therapeutic efficacy of saffron. CS-AuNPs were characterized as spherical particles of 11–20 nm size, showing strong absorption properties. The anti-depressant effects of saffron are attributed to its active components such as crocins, crocetin, and safranal, which have been known to modulate brain monoamine levels. These compounds were found to influence emotions, thoughts, and cognitive functions affected by depression. Additionally, saffron has been demonstrated to reduce the expression of proinflammatory cytokines (IL-1β, IL-6, TNF-α) and inhibit NF-κB activation, indicating potential anti-inflammatory effects in depression. This novel approach underscores the promising therapeutic potential of saffron in treating depression, providing a safe and effective alternative to conventional antidepressant therapies (Li et al. 2024).

A study indicated that crocetin, a key component of saffron, could help manage depressive-like symptoms caused by chronic stress by reducing oxidative damage in the brain. In the study, rats subjected to chronic restraint stress exhibited increased immobility time and decreased activity levels, indicative of depression. However, treatment with crocetin significantly improved these behaviors, suggesting an antidepressant effect. Additionally, crocetin normalized the levels of MDA and GSH, and restored the activities of antioxidant enzymes to normal levels in the stressed rats. These findings highlighted crocetin's potential in alleviating depression by mitigating oxidative damage and enhancing antioxidant defenses in the brain. Therefore, crocetin offered a promising natural approach for the treatment of stress-induced depression (Farkhondeh et al. 2018). The research focused on evaluating saffron's impact on depression and its neuroprotective as well as pharmacological effects on intestinal function in mice subjected to chronic restraint stress. Crocetin mitigated depressive-like behaviors in the mice experiencing chronic restraint stress. It significantly reduced elevated MKP-1, proBDNF, alanine transaminase, and aspartate transaminase levels, while increasing serum DA and CREB levels. It protected hippocampal neurons and partially restored intestinal microbiota composition. These findings underscore crocetin's neuroprotective effects against stress-induced brain damage by modulating the MKP-1-ERK1/2-CREB pathway and the intestinal ecosystem (Lin et al. 2021). The anti-depressant effects of saffron, specifically through its active compound crocetin, were investigated in mice subjected to chronic restraint stress (CRS). Crocetin administration (20, 40, and 80 mg/kg, intraperitoneal injection) rapidly alleviated depressive-like behaviors within 3 h of treatment, sustaining its effects for up to 2 days. Histological analyses indicated that crocetin mitigated hippocampal neuroinflammation and neuronal damage associated with depression-like phenotypes. Furthermore, crocetin significantly reduced serum levels of inflammatory factors, corticosterone, and pro-brain-derived neurotrophic factor compared to CRS-induced mice. Western blot analyses revealed that crocetin downregulated mitogen-activated kinase phosphatase 1 and toll-like receptor 4 levels, while upregulating expressions of extracellular signal-regulated kinase 1/2 (ERK1/2), cAMP-response element binding protein, and various phosphorylated signaling molecules including PI3K/AKT pathway components. These findings suggest that crocetin exerts rapid antidepressant effects by modulating inflammatory responses and neuronal apoptosis through PI3K/AKT signaling pathways (Lin et al. 2024).

A study aimed to investigate the antidepressant effects of crocin-1, a primary active compound in saffron, on mice subjected to chronic unpredictable mild stress (CUMS). The research found that crocin-1 administration significantly mitigated CUMS-induced weight loss and improved depressive-like behaviors in mice. Specifically, oral doses of crocin-1 (10, 20, and 40mg/kg) increased latency and reduced immobility time in both tail suspension and forced swimming tests. Furthermore, crocin-1 restored decreased levels of the neurotransmitters dopamine (DA) and serotonin (5-HT) in the serum, increased mature brain-derived neurotrophic factor (mBDNF) levels, and reduced proBDNF levels. The treatment also decreased MKP-1 mRNA and protein expression in the hippocampus while increasing the expression of BDNF and CREB mRNA. These results suggest that crocin-1 exerts antidepressant-like effects in the CUMS model of depression in mice by regulating neurotransmitters and activating the MKP-1/CREB/BDNF pathway, thereby balancing proBDNF and mBDNF levels (Wang et al. 2019). Crocin effectively alleviated anxiety and depression induced by unpredictable chronic mild stress (UCMS) in rats. UCMS had elevated stress hormones (corticosterone) and increased oxidative stress and inflammation markers in the brain, while reducing antioxidant enzymes and BDNF levels in cortical tissues. Crocin reversed these effects, enhancing behavioral outcomes in tests like open field, elevated plus maze, and forced swimming tests. Crocin mitigated oxidative stress by reducing MDA and inflammatory cytokines such as TNF-α and IL-6. It also boosted antioxidant enzyme activity (SOD, CAT, thiol) and increased BDNF expression in the cortex, promoting neuroprotection and synaptic function critical for mood regulation, highlighting crocin's potential as a therapeutic agent against stress-related anxiety and depression (Abbaszade-Cheragheali et al. 2022).

The anti-depressant effects of saffron, specifically its carotenoids Crocin and Crocetin, were investigated in rats subjected to unpredictable chronic mild stress (UCMS). Both compounds alleviated depression and anxiety symptoms as confirmed by various behavioral tests. They significantly increased serum serotonin levels and reduced corticosterone levels in depressed rats. In the hippocampus, Crocin and Crocetin enhanced the expression or increased the ratios of signaling molecules involved in mood regulation such as CREB, ERK, BAD, BDNF, p11, and 5-HT1B. Additionally, they reduced the expression of NR2B and FOXO3a, indicating a potential regulatory effect on NMDA receptor function. Bioinformatics analysis suggested that Crocin and Crocetin bind to the serotonin transporter (SLC6A4) and NR2B subunit of the NMDA receptor, similar to Fluoxetine. Crocetin was shown to inhibit NMDA receptor function in hippocampal neurons, potentially contributing to its antidepressant mechanism (Mohammadi et al. 2023). The anti-depressant effects of saffron were evidenced in an animal model of depression induced by social isolation. Affron®, a standardized saffron extract rich in safranal and crocin isomers, was administered orally and intraperitoneally. Behavioral tests including the elevated plus maze, forced swimming test, and sucrose preference test demonstrated improvements in anxious and depressive states. Specifically, animals receiving oral affron® showed increased consumption of a sweet solution, indicative of restored pleasure or motivation, and exhibited enhanced escape responses in the forced swimming test, suggesting reduced behavioral despair. These findings underscore the potential of oral saffron supplementation in alleviating symptoms associated with anxiety and depression (Orio et al. 2020).

Thus, Saffron and its active compounds, particularly crocetin and crocin, show promising anti-depressant effects in animal models subjected to various stressors like chronic restraint stress, unpredictable mild stress, and social isolation. These studies consistently demonstrate saffron's ability to improve depressive behaviors through mechanisms such as neurotransmitter modulation (serotonin, dopamine), enhanced BDNF expression, and reduction of inflammation and oxidative stress. Saffron also influences critical signaling pathways involved in mood regulation, such as MAPK-CREB-BDNF and PI3K/AKT pathways, essential for neuronal survival and synaptic plasticity. These findings highlight saffron as a potential natural treatment for depression, offering advantages over conventional antidepressants due to its safety profile and multifaceted pharmacological actions. Further clinical research is needed to confirm these pre-clinical findings and explore saffron's efficacy in human depression management.

Clinical insights into Saffron's antidepressant effects

This section reviews clinical studies investigating the antidepressant effects of saffron and its bioactive constituents, crocin, and crocetin, in diverse patient populations. Table 3 summarizes these studies, highlighting study design, treatment protocols, and key outcomes. Saffron demonstrated significant antidepressant effects in post-menopausal women with MDD associated with hot flashes. The study involved sixty women who received either saffron (30 mg/day) or a placebo for six weeks. Results indicated a significant improvement in depressive symptoms as measured by the Hamilton Depression Rating Scale (HDRS) in the saffron group compared to the placebo group. The findings suggest that saffron is an effective and safe non-hormonal alternative for treating depression and hot flashes in post-menopausal women, with fewer side effects (Kashani et al. 2018). Saffron exhibited significant antidepressant potential in a study involving patients with major depressive disorder accompanied by anxious distress. Sixty-six patients were randomly assigned to receive either saffron (30 mg/day) or citalopram (40 mg/day) for six weeks. The Hamilton Rating Scale for Depression (HAM-D) and the Hamilton Rating Scale for Anxiety (HAM-A) were used to assess treatment effects. Results indicated significant improvements in both depression and anxiety scores for patients in both groups. Comparison between the saffron and citalopram groups showed no significant difference in score changes. The frequency of side effects was also not significantly different between the two groups, suggesting that saffron is an efficacious and tolerable treatment option for major depressive disorder with anxious distress (Ghajar et al. 2017).

A study aimed to assess the efficacy of crocin, a key constituent of saffron, as an adjunctive treatment for major depressive disorder (MDD). The randomized, double-blind, placebo-controlled pilot trial involved 40 MDD patients aged 24 to 50. Participants were divided into two groups: one received a selective serotonin reuptake inhibitor (SSRI) plus crocin tablets (30 mg/day), and the other received an SSRI plus placebo. After four weeks, the crocin group showed significantly improved scores on the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and General Health Questionnaire (GHQ) compared to the placebo group. These results suggest that crocin has a significant antidepressant effect and could be beneficial in treating MDD patients (Talaei et al. 2015). A study investigated the effects of saffron on MDD in older adults, comparing it with sertraline. The double-blind, randomized intervention included 50 older outpatients with MDD (mean age 65 years; 70% male) who received either saffron (60 mg/day) or sertraline (100 mg/day) for six weeks. Depression severity was assessed using the Hamilton Depression Rating Scale (HDRS) at baseline, week 2, week 4, and week 6. The results showed that symptoms of depression significantly decreased over time in both groups, with no significant differences between the saffron and

Table 3 Clinical studies on saffron's antidepressant effects

Study title	Study design	Treatment protocol	Key outcomes	References
Crocin as Adjunctive Treatment in MDD	Randomized, double-blind, placebo-controlled pilot clinical trial	Crocin (30 mg/day) + SSRI vs. Placebo + SSRI for 4 weeks	Significant improvements in BDI, BAI, and GHQ scores in the crocin group compared to the placebo group	(Talaei et al. 2015)
Saffron vs. Sertraline in Older Adults with MDD	Double-blind, randomized intervention study	Saffron (60 mg/day) vs. Sertraline (100 mg/day) for 6 weeks	Both treatments significantly reduced HDRS scores over time with no significant difference between groups	(Ahmadpanah et al. 2019)
Curcumin and Saffron Combination in MDD	Randomized, double-blind, placebo-controlled study	Placebo, Low-dose curcumin (250 mg b.i.d.), High-dose curcumin (500 mg b.i.d.), Low-dose curcumin + Saffron (15 mg b.i.d.) for 12 weeks	Combined curcumin/saffron led to significant improvements in IDS-SR30, STAI-state, and STAI-trait scores compared to placebo	(Lopresti and Drummond 2017)
Saffron in MDD with Hot Flashes	Randomized controlled trial	Saffron (30 mg/day) vs. Placebo for 6 weeks	Significant improvements in HFRDIS and HDRS scores in the saffron group compared to the placebo	(Kashani et al. 2018)
Saffron vs. Citalopram in MDD with Anxious Distress	Randomized controlled trial	Saffron (30 mg/day) vs. Citalopram (40 mg/day) for 6 weeks	Significant improvements in HAM-D and HAM-A scores in both groups with no significant difference between treatments	(Ghajar et al. 2017)

sertraline treatments. This suggests that saffron is an effective antidepressant for older adults, providing a viable alternative to synthetic drugs (Ahmadpanah et al. 2019). A randomized, double-blind, placebo-controlled study assessed the antidepressant effects of saffron, both alone and in combination with curcumin, on individuals with major depressive disorder (MDD). 123 participants were assigned to one of four treatment groups: placebo, low-dose curcumin (250 mg b.i.d.), high-dose curcumin (500 mg b.i.d.), or low-dose curcumin plus saffron (15 mg b.i.d.) for 12 weeks. The study measured outcomes using the Inventory of Depressive Symptomatology self-rated version (IDS-SR30) and Spielberger State-Trait Anxiety Inventory (STAI). Results indicated that active treatments (combined curcumin and saffron) led to significantly greater improvements in depressive symptoms compared to placebo, and significantly better STAI-state and STAI-trait scores. The response rates for people with atypical depression were higher (65%) compared to the general group (35%). There were no significant differences between the varying doses of curcumin or the curcumin/saffron combination. Thus, the study demonstrated that saffron, particularly when combined with curcumin, effectively reduced depressive and anxiolytic symptoms in individuals with MDD (Lopresti and Drummond 2017).

The studies collectively provide robust evidence supporting the antidepressant effects of saffron across different demographics and conditions. Saffron's efficacy in alleviating depressive symptoms has been demonstrated in post-menopausal women, individuals with MDD accompanied by anxious distress, and older adults, as well as in combination treatments with curcumin. The mechanism of action of saffron's antidepressant effects is believed to be related to its active constituents, such as crocin, which influence serotonin levels in the brain. This aligns with the findings from multiple studies showing significant improvements in depression and anxiety scores among patients treated with saffron, whether alone or as an adjunctive therapy. For instance, the addition of crocin to SSRIs resulted in notable enhancements in both depressive and anxiety symptoms, suggesting a synergistic effect that enhances overall treatment efficacy. Hence, the accumulated evidence strongly supports saffron as a potent, safe, and effective treatment for MDD. Its versatility across various patient demographics and potential in combination therapies opens new avenues for the management of depression, aligning with a growing preference for natural and holistic approaches in mental health care.

Challenges and future insights

Saffron (*Crocus sativus* L.) has gained significant attention as a natural intervention for MDD, offering multifaceted pharmacological effects with a favorable safety profile. However, despite promising clinical and preclinical evidence, several critical challenges must be addressed before saffron can be fully integrated into mainstream psychiatric care. These challenges range from standardization and quality control to bioavailability limitations, long-term safety concerns, and the need for precision medicine approaches. Future research should focus on refining saffron's clinical applications, enhancing its therapeutic efficacy, and identifying key molecular pathways that contribute to its antidepressant effects. One of the most significant hurdles is standardization and quality control. The therapeutic efficacy of saffron depends on its bioactive components, particularly crocin, crocetin, safranal, and picrocrocin. However, the concentrations of these compounds vary based on geographic origin, cultivation conditions, extraction methods, and post-harvest processing. Environmental factors such as soil composition, climate variations, and agricultural practices influence the phytochemical profile of saffron, potentially leading to inconsistencies in its pharmacological effects. Additionally, adulteration and contamination remain significant concerns, as saffron is one of the most frequently adulterated spices worldwide. Standardized formulations with well-characterized chemical compositions, optimized extraction protocols, and rigorous quality control measures are essential to ensure reproducibility, consistency, and therapeutic reliability. Implementing advanced analytical techniques such as liquid chromatography-mass spectrometry (LC–MS), nuclear magnetic resonance (NMR) spectroscopy, and high-performance liquid chromatography (HPLC) could help verify the authenticity and purity of saffron extracts, minimizing variability across clinical studies. Beyond standardization, the precise molecular mechanisms underlying saffron's antidepressant effects remain incompletely understood. While it is well-documented that saffron modulates serotonin, dopamine, and noradrenaline neurotransmission, its broader impact on neuroimmune regulation, oxidative stress, neurotrophic signaling, and gut-brain axis interactions requires further elucidation. Recent advances in transcriptomics, proteomics, and metabolomics could provide deeper insights into how saffron modulates neuronal plasticity, synaptic remodeling, and inflammatory pathways in depression. Additionally, pharmacokinetic and pharmacodynamic profiling, including studies on saffron's blood–brain barrier permeability, metabolic transformation, and systemic clearance, is crucial for optimizing dosing regimens and maximizing therapeutic efficacy. A particularly promising yet underexplored area is saffron's modulation of gut microbiota and its role in the microbiota-gut-brain axis. Emerging evidence suggests that gut dysbiosis plays a role in MDD pathophysiology, and saffron may exert its antidepressant effects in part by enhancing microbial diversity, increasing SCFA production, and improving gut barrier integrity. Clinical trials incorporating microbiome profiling, metagenomic sequencing, and fecal metabolomics are needed to confirm these effects and establish whether saffron interacts with specific microbial taxa associated with mental health resilience. Furthermore, combinatorial therapies involving saffron and probiotics, prebiotics, or dietary interventions could provide novel treatment strategies for depression by targeting both neurotransmitter systems and gut microbiota. Another major challenge is saffron's bioavailability and metabolic stability. Like many plant-derived compounds, saffron's key constituents undergo extensive first-pass metabolism, enzymatic degradation, and limited systemic absorption. This may reduce its clinical efficacy, particularly when administered orally. To overcome these limitations, novel drug delivery systems such as nanoencapsulation, liposomal formulations, and polymer-based controlled-release carriers have been proposed to enhance saffron's pharmacokinetics, tissue penetration, and CNS bioavailability. Advances in nanotechnology-based formulations, lipid-based nanoparticles, and transdermal delivery systems could play a transformative role in optimizing saffron's therapeutic potential. Future research should focus on developing pharmacokinetically optimized saffron extracts that can achieve higher brain concentrations with sustained release properties, thereby enhancing its antidepressant effects. Additionally, personalized medicine approaches may be critical for maximizing saffron's therapeutic benefits and minimizing interindividual variability in treatment responses. The antidepressant effects of saffron are likely influenced by genetic polymorphisms, metabolic pathways, and gut microbiota composition. For instance, polymorphisms in SLC6A4, BDNF genes, and inflammatory cytokine-related genes may determine an individual's response to saffron supplementation. Integrating pharmacogenomics, microbiome sequencing, and machine learning-driven predictive modeling into future clinical studies could help identify biomarkers predictive of saffron's efficacy. Such personalized approaches could enable precision-targeted interventions that optimize saffron's antidepressant potential in specific patient populations. Despite its favorable safety profile, further research is needed to establish long-term safety, optimal dosing, and potential interactions with conventional antidepressants. Most clinical trials have been relatively short in duration, typically lasting 6 to 12 weeks. There is currently limited data on the long-term effects of chronic saffron supplementation, including potential risks of tolerance, withdrawal effects, or drug interactions. Large-scale, multicenter, long-duration studies are required to determine whether saffron maintains its efficacy over extended treatment periods and whether it can be safely combined with SSRIs, SNRIs, MAOIs, or other psychiatric medications. Another emerging area of research is the integration of saffron into holistic treatment approaches for MDD. Depression is a multifactorial disorder influenced by genetic, neurobiological, psychological, and lifestyle factors. While pharmaceutical interventions play a crucial role, non-pharmacological strategies such as dietary modifications, exercise, mindfulness, and cognitive-behavioral therapy (CBT) are increasingly recognized as essential components of comprehensive mental health care. Given saffron's neuroprotective, anti-inflammatory, and antioxidant properties, it could be incorporated into broader lifestyle-based interventions alongside omega-3 fatty acids, polyphenol-rich diets, and structured exercise regimens. For example, dietary patterns rich in anti-inflammatory and antioxidant compounds could complement saffron's mood-enhancing effects, while physical activity, known to upregulate BDNF, could further amplify its impact on neuroplasticity and resilience to stress. In addition to depression treatment, saffron's potential applications in neurodegenerative diseases, cognitive enhancement, and age-related mental health disorders warrant further exploration. Preclinical studies suggest that saffron may protect against Alzheimer's disease, Parkinson's disease, and age-related cognitive decline by reducing amyloid-beta aggregation, oxidative stress, and neuroinflammation. However, longitudinal clinical trials are necessary to determine whether saffron-based interventions can delay cognitive deterioration or enhance cognitive function in at-risk populations.

In summary, while saffron represents a compelling natural intervention for depression, significant challenges remain in standardization, pharmacokinetics, precision medicine applications, and long-term clinical validation. Addressing these gaps through systematic scientific investigation, advanced drug delivery technologies, and personalized treatment approaches will be essential in fully unlocking saffron's therapeutic potential. If these challenges are met, saffron may not only emerge as a viable alternative to conventional antidepressants but as a versatile therapeutic agent with applications across psychiatry, neurology, and integrative medicine. Future research should focus on bridging the gap between traditional medicine and modern psychopharmacology, ensuring that saffron is positioned as a scientifically validated, evidence-based intervention for mental health care.

Conclusions

Saffron (*Crocus sativus* L.) has gained increasing recognition as a promising natural treatment for MDD, demonstrating significant antidepressant effects across preclinical and clinical studies. Evidence from randomized controlled trials (RCTs) supports its efficacy in alleviating depressive symptoms, with some studies indicating comparable effects to conventional antidepressants such as SSRIs. Importantly, saffron appears to offer a favorable safety profile, fewer side effects, and better tolerability compared to synthetic antidepressants, making it a particularly attractive option for individuals seeking natural or adjunctive therapies. The antidepressant effects of saffron are attributed to its ability to modulate neurotransmitter systems (serotonin, dopamine, norepinephrine), enhance neuroplasticity, reduce oxidative stress, suppress neuroinflammation, and regulate gut microbiota. However, gaps remain in understanding its precise molecular mechanisms, long-term efficacy, and optimal dosing strategies. Standardization of saffron extracts, pharmacokinetic profiling, and large-scale clinical validation will be essential in confirming its role in mainstream psychiatric care. Future research should focus on multicenter, long-duration clinical trials to establish saffron's sustained efficacy, optimize personalized treatment approaches, and explore its integration into holistic lifestyle-based interventions. Investigating its synergistic effects with probiotics, prebiotics, and neurotrophic compounds may provide additional insights into its therapeutic versatility. Innovative delivery systems, including nanotechnology-based formulations, could further enhance saffron's bioavailability and therapeutic impact. Overall, saffron represents a valuable and multifaceted approach to depression management, bridging the gap between traditional medicine, modern neuroscience, and integrative psychiatry. Continued scientific exploration and clinical validation will be crucial in establishing saffron as a mainstream therapeutic option, ensuring that patients have access to safe, effective, and well-tolerated treatments for MDD and related mood disorders.

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