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The Impact of Saffron Crocin on Clinical and Psychological Complications of Opioid Substance Withdrawal Syndrome: A Systematic Review of *in vivo* and clinical trial studies

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Abstract

Background & Objectives: Drug addiction constitutes a global issue associated with severe personal, economic, social, and health problems. Saffron, an herbal medicine, has demonstrated potential therapeutic applications for mental and physical symptoms. This review assesses the efficacy of saffron crocin in managing the clinical and psychological complications of opioid substance withdrawal syndrome(OWS).

Materials & Methods: The research methodology entailed a comprehensive literature review spanning from 2010 to 2023, utilizing databases such as Scopus, PubMed, Embase, and Web of Science. The search focused on the impact of saffron crocin on clinical and psychological complications of OWS. Human randomized controlled trials (RCTs) and animal studies published in English were included for data synthesis. Subsequently, information was collated based on the following parameters: study author, number of studies, dosage, control group, duration, outcome criteria, and primary outcomes.

Results: Eight articles were analyzed, demonstrating the efficacy of saffron and crocin in treating OWS by ameliorating withdrawal symptoms and improving laboratory indicators.

Conclusion: While several RCTs support the effectiveness of saffron crocin in alleviating OWS symptoms, further rigorous studies are warranted to corroborate these findings.

Keywords: Crocin, Substance Withdrawal Syndrome, Complications, Psychological Phenomena, Systematic Review

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Introduction

Opioid abuse disorder constitutes a significant global socio-economic and clinical concern (1). Several classes of substances, including opioids, tobacco, alcohol, barbiturates, and sedatives, are frequently abused and documented to induce deprivation syndrome (2). Tobacco smoking represents one of the major risk factors for chronic diseases such as cardiovascular disease, cancer, and type 2 diabetes mellitus (3).

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Withdrawal syndrome manifests when there is a reduction in the blood or tissue concentration of a substance in individuals who have chronically consumed large quantities of said substance. While the symptoms associated with withdrawal from different substances exhibit unique characteristics, certain common symptoms are observed across various substances (4). Symptoms of withdrawal include, but are not limited to, rhinorrhea, increased lacrimation, myalgia, diarrhea, nausea, vomiting, pupillary dilation, insomnia, tachycardia, hypertension, sweating, tachypnea, anxiety, irritability, and hyperreflexia (5). Methadone maintenance treatment (MMT) is considered the most cost-effective approach for managing opioid dependence. This treatment modality offers both benefits and side effects to the individuals undergoing it (6). One mechanism by which methadone improves overall and mental health in addicts is through inhibition of serotonin reuptake. Saffron exhibits a similar mechanism and additionally possesses anti-inflammatory and analgesic properties. Prior research has confirmed these effects of saffron, prompting the hypothesis that it could serve as a beneficial adjunct therapy to reduce methadone dosage (7).

Herbal medicines, such as saffron, have gained popularity due to their fewer side effects compared to chemical medications (8). Known to most as saffron, *Crocus sativus* L. (*C. sativus*) is a small perennial plant belonging to the *Iridaceae* family. Numerous countries, including Iran, Afghanistan, Turkey, and Spain, cultivate this plant (9). Saffron, which has been utilized for its medicinal properties since ancient times across various regions of the world (10), comprises several bioactive compounds, including safranal, picrocrocin, and crocin. Among these, crocin serves as the primary antioxidant in saffron and contributes to its distinctive coloration (11). Saffron and crocin have been associated with potential benefits for central nervous system function and psychological well-being by regulating the production of important neurotransmitters in the brain, such as dopamine, serotonin, and norepinephrine (5-hydroxytryptamine) (6). The antidepressant effect of saffron is attributed to crocin and safranal. Crocin affects the dopaminergic system and prevents the reabsorption of norepinephrine, while safranal influences the serotonergic system (8). Studies suggest that crocin can increase dopamine levels and protect dopaminergic neurons (12). Evidence from both animal and clinical studies suggests that saffron and/or its active constituents decrease depression, anxiety, pain, insomnia, obsessive-compulsive disorder, the severity of premenstrual syndrome, neuropathic pain responses, human monoamine oxidases, sexual dysfunction, morphine-induced conditioned place preference (CPP), the severity of precipitated morphine withdrawal, and the development of morphine tolerance in neuropathic pain. Additionally, saffron and its constituents have been shown to enhance morphine-induced antinociception, as well as learning and memory (13). This study evaluates the impact of saffron crocin on clinical and psychological outcomes of opioid substance withdrawal syndrome (OWS) with the objective of reducing withdrawal symptoms.

Materials and Methods

Literature Search and Study Selection

This study focused on investigating the efficacy of saffron crocin in managing withdrawal symptoms in individuals with opioid or opium abuse. A comprehensive literature search was conducted using PubMed, Web of Science, Scopus, and Embase databases, covering the period from January 2010 to August 2023. The search terms employed included “crocin” or “saffron” and “withdrawal syndrome” or “withdrawal symptoms” and “opium” or “morphine” or “heroin” or “methadone” or “codeine.” Only English-language articles were considered for inclusion.

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Inclusion and Exclusion Criteria

Study Design

Reviews, editorials, conference papers, observational studies, case reports, and case series were excluded from consideration, along with any irrelevant articles.

Interventions

Any form of saffron (powder, extract, or oil) was included. Studies that examined saffron in combination with other ingredients or evaluated the effect of an isolated active component of saffron were excluded.

Control

Studies that compared saffron with placebo, no treatment, or conventional treatments were included.

Article Search

Two authors independently conducted bibliographic searches, article selection, and data extraction, adhering to the standard protocols for reporting systematic reviews outlined in the 2009 PRISMA checklist. Any disagreements between the authors were resolved prior to proceeding with data processing.

Quality Assessment

The risk of bias was evaluated independently by two authors using the Cochrane Collaboration's recommended tool (14). Six types of bias were assessed accordingly: selection bias (random sequence generation and allocation concealment), performance bias and detection bias (blinding), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other bias. Each item was categorized as "low," "unclear," or "high risk" of bias. A low risk of bias was assigned if a trial met all criteria; a high risk of bias was assigned if a trial met none of the criteria; and an unclear risk of bias was assigned if a trial provided insufficient information for judgment. Any disagreement regarding the risk of bias assessment was discussed and resolved through consultation with a third author.

Data Extraction

Data and variables were collated as follows: general information, including the author's name, publication date, and details of the investigated participants, was extracted. Additionally, the study gathered and analyzed quantifiable factors and documented results.

Data Analysis

The information was described qualitatively, and the differences in the levels of the factors were evaluated against the control groups in each specific study.

Results

General Information: Following a comprehensive review of studies and adherence to inclusion criteria, a total of 114 articles were initially identified. Subsequent removal of duplicates and restriction to full-text English articles yielded 32 relevant publications. After excluding irrelevant documents, observational studies, case series, and case reports, 8 randomized controlled trials (RCTs) and animal studies were selected for data collection. The process of article selection is depicted in Figure 1. The selected studies examined the comparative effects of saffron-crocin in relation to methadone and placebo. Study durations ranged from 30 minutes in laboratory-based articles to 12 weeks in clinical trials. Clinical trials were conducted exclusively in Iran and Afghanistan. Table 1 provides a summary of the articles. All studies demonstrated that saffron-crocin administration led to a significant reduction in OWS. In the study conducted by Abbaszadeh Meshkani et al., the effects of crocin were investigated, revealing side effects such as headaches, nausea, restlessness, and urinary incontinence among participants in the treatment group (15).

Discussion

This systematic review examined the effects of saffron-crocin on the clinical and psychological consequences associated with OWS, based on a comprehensive analysis of 8 published articles.

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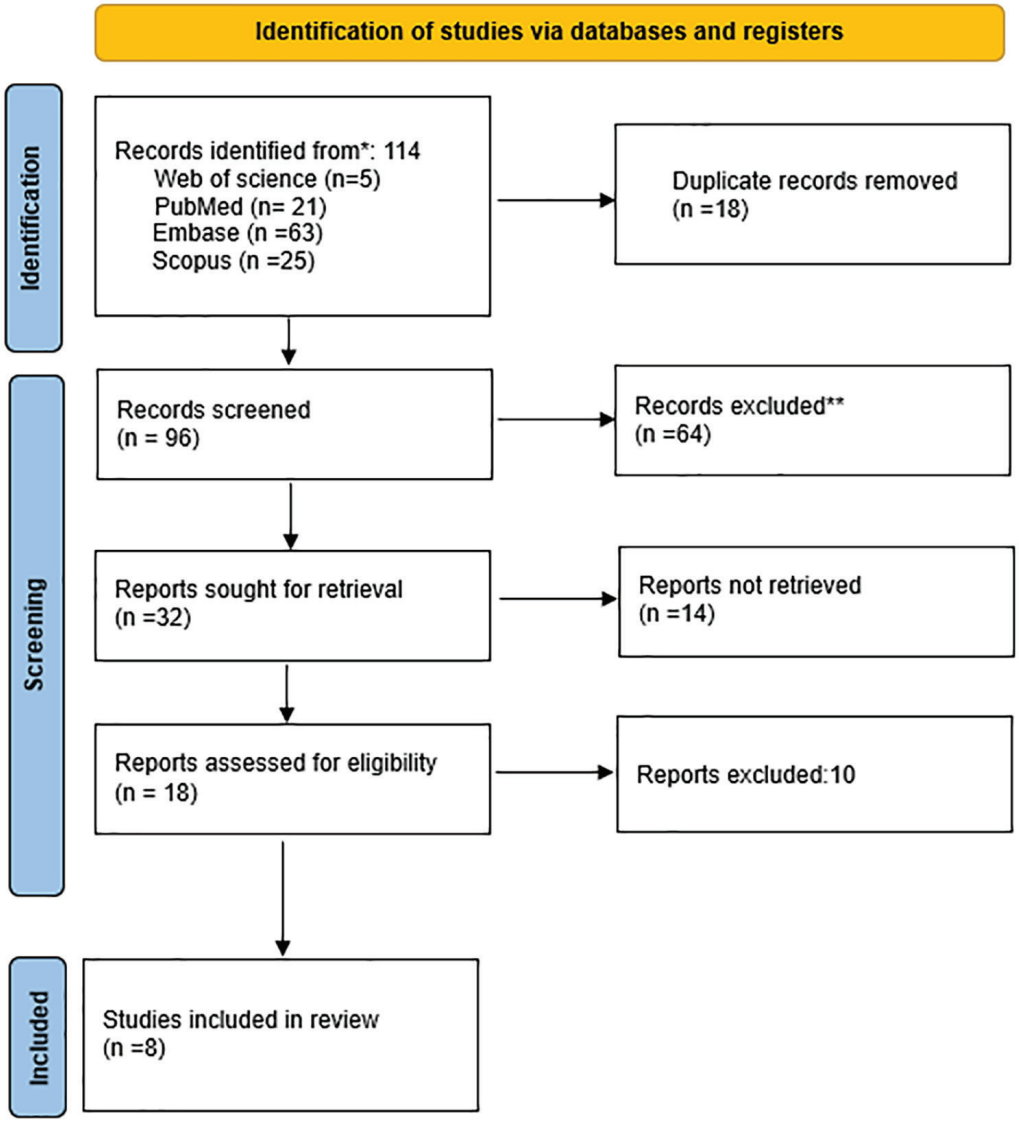

Figure 1. The PRISMA 2020 flowchart depicts the process of identification and selection relevant studies from databases and registers.

Effect on Withdrawal Symptoms and Cravings

Saffron demonstrated efficacy in alleviating withdrawal symptoms such as headache, nausea, irritability, and urinary incontinence, as well as reducing cravings in individuals with substance withdrawal syndrome (15). Additionally, it was found to mitigate symptoms including diarrhea, rhinorrhea, myalgia, temptation, and anorexia during withdrawal (7). The positive impacts of saffron on easing physical symptoms of morphine withdrawal syndrome were documented (17). Furthermore, Shaja et al. reported the effectiveness of saffron and crocin in managing symptoms of ethanol withdrawal syndrome in mice (19). The saffron aqueous extract was shown to reduce withdrawal scores, psychological dependency, and voluntary morphine intake in a mouse model of morphine dependence experiencing relapse or undergoing withdrawal. These findings of a modest reduction in withdrawal signs by saffron extract are consistent with previous research from the

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Table 1. Summary of included articles

Study (author, year)	Number Of Cases	Dose	Control	Duration	Outcomes criteria	Main Outcome
Abbaszadeh Meshkani 2020 (15)	60 patients (30-30)	crocin (active substance of saffron) 15 mg orally BID	placebo	12 weeks	Enthusiasm score, withdrawal symptoms score, cognitive parameters (TMT route construction test, FAS verbal fluency test), DGSP criterion	Significant improvement in craving score ($p<0.05$) and withdrawal symptoms score ($p<0.05$) No significant effect on cognitive parameters
Nemat Shahi 2017 (7)	44 patients	Saffron (capsule 30 mg)	placebo	8 weeks	Withdrawal symptoms: diarrhea, rhinorrhea, myalgia, Temptation and anorexia	The daily dose of methadone significantly reduces withdrawal symptoms (diarrhea, rhinorrhea, myalgia) Reduced temptation and anorexia
Khalatbari 2019 (6)	50 patients (25-25)	2 doses of 15 mg crocin	placebo	8 weeks	Beck depression Beck anxiety general health, Pittsburgh Sleep Quality	Reducing depression and anxiety, improving general health, sleep quality and sexual performance
Jomehpour 2022 (16)	72 patients	two times a day (15 mg)	placebo	6 weeks	Abstinence and cravings Depression, Stress, anxiety	No effect
Ghaderi 2019 (1)	53 patients (26-27)	15 mg/day	placebo	8 weeks	Beck anxiety, Beck depression, Clinical responses, metabolic and genetic profiling	Improving mental health and metabolic profile
Kiashemshaki 2021 (13)	rats	60 mg/kg	Normal saline	10 days	Spontaneous withdrawal symptoms, anxiety, depression, voluntary use of morphine	Reduced withdrawal symptoms No effect on depression and anxiety Reduced morphine use
Hosseinzadeh (17) 2010	10 groups of 8 mice	40-80 mg/kg	Normal saline	3 days	Withdrawal symptoms such as motor activity	Both water-based and alcohol-based saffron extracts were found to decrease withdrawal symptoms
Akbari 2020 (18)	30 rats	100-150-200 mg/kg	-	30 minutes after naloxone injection	Withdrawal symptoms (muscle twitching, teeth grinding, paw tremors, licking and chewing)	Reduction of withdrawal symptoms after consuming aqueous extract of Afghan saffron

BID: bis in die, twice a day , TMT: Trail making test , FAS: verbal fluency test , DGSP: straight digit span

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case group. Prior studies demonstrated that both aqueous and ethanolic extracts of saffron, or their isolated components, mitigated the severity of naloxone-induced morphine withdrawal symptoms, including jumping behavior (13, 18). Moreover, saffron administration led to reduced motor activity in mice (17).

Effect on Cognitive Parameters

In the study by Abbaszadeh and colleagues, saffron did not exhibit a significant impact on cognitive parameters (15). Conversely, laboratory and animal evidence has highlighted the favorable effects of crocin on cognitive performance (20, 21).

Effect on Depression, Anxiety, and Mental Health Parameters

Crocin supplementation was found to impact mental health indicators and metabolic profiles in patients undergoing treatment with methadone maintenance. In a randomized clinical trial, the use of crocin led to a notable reduction in Beck Depression Inventory and Beck Anxiety Inventory scores when compared to a placebo (1, 6). Similarly, crocin has demonstrated the ability to lower levels of anxiety and depression in mood disorders, metabolic syndrome, and postpartum depression (22-25). The exact mechanism underlying the effect of crocin on depression and anxiety remains unknown; however, its potent antioxidant properties may prevent free radical damage and enhance mental well-being (26). An animal study indicated that saffron did not alleviate depression and anxiety-like symptoms caused by morphine dependency within 10 days. Nonetheless, over a 30-day period, saffron was effective in reducing anxiety and depressive symptoms in these animal models. We also found that extract administration for a period of 30 days attenuated anxiety and depressive-like behaviors in rats undergoing morphine withdrawal. Therefore, it might be assumed that this discrepancy can be explained, in part, by differences in the duration of extract administration (12 days vs. 30 days) (13).

In a 12-week randomized, double-blind study, Lopresti and associates examined 123 patients. They found that patients with major depressive disorder experienced a reduction in their symptoms of depression and anxiety by utilizing different dosages of curcumin and a combined curcumin/saffron treatment (27). Similarly, Mazidi et al. discovered that patients taking 50 mg of saffron (b.i.d.) for 12 weeks exhibited fewer depressive and anxiolytic symptoms than those in the placebo group (28).

Effect on Sleep Quality

Studies have demonstrated that crocin improves sleep disturbances in methadone-treated patients (6). The role of saffron in sleep quality is attributed to the crocin and safranal compounds present in saffron, which impact the dopaminergic and serotonergic systems, inhibit epinephrine reuptake, and exhibit activity similar to sleep aids (29, 30). Kell et al. reported that saffron doses of 22 mg and 28 mg per day for four weeks significantly enhanced sleep quality in healthy individuals (23). In a separate study, diabetic patients experienced positive effects in terms of decreased anxiety and improved sleep quality following a 7-day saffron treatment (31). In an animal study conducted by Masaki et al., crocin was observed to prolong the duration of non-rapid eye movement sleep (non-REM sleep) in mice (32).

Effect on Sexual Performance

Research findings suggest that crocin enhances sexual performance (6). Improved sexual activities have been observed in diabetic patients and individuals with major depression (33, 34). Additionally, crocin supplementation for 12 weeks decreased cravings and withdrawal symptoms in MMT patients. Furthermore, crocin improved the International Index of Erectile Function scores in male patients.

Effect on Laboratory Indicators

Crocin supplementation led to a reduction in Fasting Plasma Glucose (FPG), insulin levels and resistance, very low-density lipoprotein cholesterol (VLDL), triglycerides (TG), and

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total cholesterol levels, while increasing insulin sensitivity (15). In a research study, crocin was found to improve various health markers, including FPG, insulin levels, Quantitative Insulin Sensitivity Check Index (QUICKI), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), TG, VLDL, high-sensitivity C-reactive protein (hs-CRP), Total Antioxidant Capacity (TAC), and Malondialdehyde (MDA) levels. Additionally, crocin supplementation resulted in reduced gene expressions of Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ), Low-Density Lipoprotein Receptor (LDLR), and Tumor Necrosis Factor-alpha (TNF-α). However, crocin did not significantly impact gene expressions of Transforming Growth Factor Beta (TGF-β) and Vascular Endothelial Growth Factor (VEGF) (1). Several studies have indicated that crocin supplementation has positive effects on inflammation and oxidative stress biomarkers, suggesting its potential therapeutic value in improving these laboratory indicators (35-38).

Although no severe adverse effects following crocin consumption have been reported, some patients experienced moderate complications including headache, insomnia, nausea, and shortness of breath (6). Notably, the study's scope was limited to English language articles, and similar studies in other languages were not included for comparison.

Conclusion

Considering the findings derived from the literature reviewed, it could be inferred that saffron, specifically crocin, exhibits potential in alleviating symptoms associated with OWS. Consequently, saffron may serve as a valuable adjunctive therapy for mitigating OWS. Nonetheless, further investigations involving high-quality randomised placebo-controlled trials incorporating larger sample sizes, extended study durations, and enhanced methodological rigor are warranted.

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Conflict of Interest

The authors declare that they have no conflicts of interest to disclose.

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Ethical Considerations

This article has been written in compliance with all applicable ethical considerations.

Code of Ethics

Not applicable.

Authors' Contribution

MT and AA contributed to the design of the manuscript. MT and VA conducted the literature search based on the keywords and performed data extraction. AB, AA, and SS verified the data extraction and composed the final report. MT and VA contributed to the drafting of the manuscript. All authors approved the final version of the manuscript.

Availability of Data and Materials

All data analyzed in this narrative review are available in the cited articles and sources. No new data were generated or analyzed as part of this review. The search strategies and criteria used to identify and select the relevant literature are described in the Methodology section.

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List of Abbreviations

- RCTs: randomized controlled trials
- MMT: Methadone maintenance treatment
- CPP: conditioned place preference Fasting Plasma Glucose (FPG
- VLDL: very low-density lipoprotein cholesterol
- TG: triglycerides
- QUICKI: Quantitative Insulin Sensitivity Check Index
- HOMA-IR: Homeostatic Model Assessment of Insulin Resistance
- hs-CRP: high-sensitivity C-reactive protein
- TAC: Total Antioxidant Capacity
- MDA: Malondialdehyde
- PPAR-γ: Peroxisome Proliferator-Activated Receptor Gamma
- LDLR: Low-Density Lipoprotein Receptor
- TNF-α : Tumor Necrosis Factor-alpha
- TGF-β: Transforming Growth Factor Beta
- VEGF: Vascular Endothelial Growth Factor
- OWS: opioid withdrawal syndrome

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