

Adjunctive Crocin for the Treatment of Withdrawal-Associated Depression in Male Methamphetamine Users: A Randomized Controlled Trial

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Abstract

Introduction

Depressive disorders are highly prevalent among individuals with methamphetamine dependence, yet integrated treatments for this dual pathology remain understudied. This trial investigated crocin's potential as an adjunct therapy for alleviating withdrawal-induced depression in males with methamphetamine use disorder.

Method

A double-blind, placebo-controlled trial enrolled 60 male participants with moderate depressive disorder secondary to methamphetamine withdrawal. Participants were randomized to either 15 mg/day crocin or placebo for 12 weeks. Depressive symptoms were assessed using BDI-II and GHQ-28 at baseline and weeks 4, 8, and 12. Statistical analyses were performed using SPSS (v26) with an $\alpha=0.05$ threshold.

Findings

Baseline characteristics were similar between groups ($P>0.05$). Both groups showed significant reductions in depression scores over time, but no statistically significant difference was observed between crocin and placebo in symptom trajectories ($*P=0.160*$). Adjusted analyses confirmed no group-by-time interaction ($*P=0.098*$ for BDI; $*P=0.369*$ for GHQ depression subscale).

Conclusion

Crocin (15 mg/day) did not outperform placebo in reducing depressive symptoms during methamphetamine/cannabis withdrawal. The findings suggest no clinically meaningful benefit of crocin as an adjunct therapy in this populatio

Keywords: Methamphetamine, Cannabis, Crocin, Major depressive disorder

Introduction

Methamphetamine, a phenylalkylamine derivative of amphetamine, is a potent psychostimulant with pronounced effects on central monoaminergic neurotransmission. Its mechanism of action involves presynaptic dopamine transporter inhibition, which potentiates synaptic dopamine concentrations while concurrently inhibiting reuptake, thereby eliciting transient euphoria, psychomotor activation, and hyperarousal. These neuropharmacological properties confer elevated abuse liability. Both acute intoxication and chronic methamphetamine use entail significant multisystemic sequelae, encompassing cerebrovascular accidents, life-threatening cardiac dysrhythmias, mood and anxiety disorders, sleep architecture disruption, psychosis, and persistent neuroplastic adaptations within corticolimbic circuitry (1).

Depression constitutes a critical public health challenge, with global burden of disease studies linking it to substantial socioeconomic costs driven largely by productivity losses within labor markets (2). The condition also strains healthcare infrastructure, as depressive symptomatology is detectable in nearly 70% of primary care patients, though comorbid cases often evade timely clinical recognition (3). Notably, in individuals with concurrent methamphetamine dependence and depression, this dual pathology portends poorer long-term outcomes and diminishes the effectiveness of standard therapeutic approaches (4).

Major depressive disorder (MDD) frequently co-occurs with substance use disorders (SUDs), compounding risks for severe outcomes such as reduced quality of life, increased disability, and greater susceptibility to suicidal behaviors (5). At the start of SUD treatment, patients with comorbid MDD often present with more severe, complex impairments—spanning physical health, legal challenges, and social instability—compared to those without MDD (6). MDD remains the most common psychiatric comorbidity in SUD populations. Population studies estimate the 12-month prevalence of MDD at 15.5% in the general public, but this rises sharply to 32.8% in individuals treated for alcohol use disorder and 44.3% in those with other SUDs (7). While some therapies show modest benefits, no psychological intervention has yet met rigorous efficacy benchmarks for this dual diagnosis. Given MDD's prevalence, clinical severity, and societal costs, pinpointing drivers of persistent symptoms and repeated relapse is critical for improving care. One overlooked factor may be the cyclical relationship between substance use and depressive symptoms over time, which could reshape integrated treatment protocols. Although theoretical frameworks suggest these symptoms interact dynamically in comorbid cases, empirical validation through longitudinal studies remains lacking (5).

Depressive disorders and substance use disorders (SUDs) frequently co-occur in clinical practice, a pattern robustly documented in psychiatric research (8). The interplay between these conditions is bidirectional: acute substance intoxication and chronic misuse disrupt neurochemical systems governing mood stability, while persistent substance use often serves as a maladaptive strategy to mitigate the burden of depressive symptoms (9). Methamphetamine exemplifies this dynamic through its unique pharmacology. Chronic methamphetamine exposure depletes dopamine and serotonin reserves in critical brain regions—such as the prefrontal cortex and striatum—fostering neurobiological vulnerability to depressive illness. Further, methamphetamine destabilizes monoamine regulation,

producing a clinical syndrome indistinguishable from major depressive disorder, including hallmark features like anhedonia, sleep-wake cycle fragmentation, and appetite dysregulation (10). Importantly, this depressive phenotype is not exclusive to methamphetamine dependence. Large-scale epidemiological studies of substances such as cocaine, heroin, alcohol, and nicotine consistently demonstrate depression rates among users that exceed population baselines by substantial margins (1).

The clinical differentiation and therapeutic management of depressive disorders among individuals with methamphetamine use pose significant diagnostic challenges, as the neuropsychiatric sequelae of intoxication and withdrawal exhibit substantial overlap with depressive symptomatology. Three clinically discrete syndromic categories require rigorous delineation during assessment:

- (a) Physiological and behavioral effects attributable to methamphetamine pharmacodynamics and withdrawal phenomena following cessation;
- (b) Depressive symptoms manifesting concomitantly with ongoing methamphetamine use;
- (c) A major depressive disorder etiopathologically distinct from methamphetamine exposure.

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) provides operationalized criteria to differentiate primary depressive disorders from substance-induced pathologies. According to DSM-5, a diagnosis of primary depressive disorder is established if either of the following conditions is met:

- Depressive symptomatology antecedes the initiation of methamphetamine use; or
- Symptoms persist beyond a duration of ≥ 4 weeks post-cessation of substance use.

Notably, DSM-5 further specifies that depressive symptoms occurring during subintoxicating or subthreshold withdrawal doses of methamphetamine similarly fulfill diagnostic criteria for a primary depressive disorder. In contrast, a substance-induced depressive disorder is diagnostically corroborated when symptoms temporally align with:

- Acute intoxication or the immediate post-intoxication phase; or
- The acute withdrawal phase of a substance with established depressogenic properties (1).

A substantial corpus of evidence underscores the deleterious impact of depressive disorders on therapeutic outcomes for substance use disorders, irrespective of whether depression is operationalized as a comorbid major depressive disorder diagnosis or quantified through longitudinal assessment of depressive symptom severity. Patients diagnosed with alcohol use disorder and comorbid major depressive disorder exhibited a markedly reduced latency to initial alcohol relapse and heightened post-treatment relapse rates following inpatient interventions (11). Notably, these studies neglected to evaluate temporal attenuation of depressive symptomatology or concomitant modifications in substance use trajectories among comorbid populations—a critical oversight given the dynamic, non-linear progression of depressive symptoms over time. The bidirectional relationship between substance use and depressive outcomes remains poorly characterized in contemporary literature... In pharmacotherapeutic trials, alcohol use disorder predicted unfavorable outcomes exclusively among patients with severe baseline alcohol consumption, while elevated baseline use correlated with diminished fluoxetine response. However, no rigorously controlled studies have mechanistically elucidated the interplay between substance use modulation and depressive symptom evolution (5).

Therapeutic strategies for concurrent methamphetamine use and depressive disorders remain empirically underexplored. Investigative efforts have focused on psychological

interventions, pharmacotherapeutic agents, and multimodal approaches for methamphetamine dependence. Among psychological modalities targeting this comorbidity, cognitive behavioral therapy (CBT) is the most extensively implemented intervention (12). Over three decades of clinical research have established CBT as a gold-standard intervention for alcohol and illicit drug dependence.

Nevertheless, its efficacy in addressing concurrent methamphetamine use and depression remains inadequately substantiated (13). A 16-week CBT trial reported a 75% reduction in methamphetamine use frequency but failed to detect statistically significant improvements in depressive symptom metrics (14). In a parallel randomized controlled trial, CBT recipients demonstrated a 50% reduction in amphetamine use over six months; however, improvements in depression severity scores were transient and non-sustained. Critically, this study did not stratify outcomes by amphetamine subtype (e.g., methamphetamine vs. dextroamphetamine), thereby precluding subtype-specific inferences (15). Aggregate evidence indicates CBT's utility in mitigating methamphetamine use but not in resolving concurrent depressive pathology.

Stepped care—a hierarchical treatment model initiating low-intensity interventions and escalating care based on therapeutic response—has shown promise in managing alcohol and substance use disorders (16). Mirroring trends observed with CBT, stepped care's applicability to comorbid methamphetamine use and depression remains conjectural. A proof-of-concept study demonstrated stepped care's capacity to attenuate depressive symptoms; however, robust validation through large-scale methamphetamine-specific cohorts is imperative (17).

A series of investigations have examined the efficacy of antidepressants in mitigating methamphetamine withdrawal, pharmacotherapeutic agents for methamphetamine dependence treatment, stimulant-based therapies for methamphetamine dependence, and nutritional supplements for concurrent depression and methamphetamine use. In randomized trials assessing antidepressant pharmacotherapy, intergroup differences in depressive symptomatology were analyzed between cohorts assigned to antidepressant or placebo regimens. Consistently, these studies demonstrated an absence of statistically significant amelioration in depressive symptoms (1).

Brown and Gabrielson disseminated outcomes from a double-blind, randomized controlled trial (RCT) evaluating the dietary supplement citicoline against placebo for bipolar or unipolar depressive disorders in methamphetamine-dependent adults. Their investigation documented a 33% reduction in depressive symptom severity—quantified via the Physician-Rated Depression Symptom Inventory—within the citicoline arm. In contradistinction, the placebo cohort exhibited a 13% reduction in clinician-assessed depression scores. Of particular note, citicoline (generic nomenclature: CDP-choline as a supplemental agent) is classified as a complementary and alternative therapeutic modality for depressive disorders. In the United States, citicoline—a naturally occurring choline derivative—is marketed as a non-prescription nutritional supplement. Beyond affective outcomes, self-reported methamphetamine usage patterns and urine toxicology testing revealed no statistically significant divergence in methamphetamine utilization from baseline to trial termination. Crucially, longitudinal analysis identified no intergroup disparities in methamphetamine use frequency or quantity during the study period. Collectively, these findings indicate citicoline's lack of therapeutic utility in addressing methamphetamine

dependence and comorbid depression. Nevertheless, validation through replication in larger samples exclusively comprising individuals with unipolar or bipolar depressive disorders remains imperative (18).

In an independent investigation evaluating the non-amphetamine psychostimulant modafinil for methamphetamine dependence intervention, researchers observed a statistically significant decline in Hamilton Depression Rating Scale (HAM-D) scores from baseline to study termination. However, throughout the 6-week trial, no alterations were identified in the incidence of positive urine toxicology assays. These outcomes warrant circumspect interpretation, as the initial cohort consisted of 8 enrollees, with merely 4 completing the protocol. Moreover, parametric statistical methodologies may be methodologically unsuited given the restricted sample size (19).

Multiple peer-reviewed studies have amalgamated pharmacotherapeutic and psychosocial modalities for methamphetamine dependence management. The preponderance of evidence suggests that combined pharmacological-psychological strategies failed to attain clinical effectiveness, with participants frequently reporting treatment-emergent adverse events. In a double-masked, placebo-controlled trial of sertraline (a selective serotonin reuptake inhibitor [SSRI]), SSRI-allocated subjects manifested persistent craving behaviors and heightened relapse incidence. Conversely, a non-randomized open-label pilot study integrating modafinil with cognitive behavioral therapy (CBT) in a cohort of HIV-seropositive males with methamphetamine use disorder revealed that treatment responders exhibited clinically meaningful reductions in depressive symptomatology across 12 weeks. Responders self-reported a >50% decrement in methamphetamine utilization frequency. Given that 55% of the cohort was undergoing antiretroviral therapy, potential neuropharmacodynamic interactions between antiretrovirals and modafinil may have mediated affective fluctuations. Notwithstanding, the external validity of these findings is substantially limited by the diminutive, homogeneous sample (n = 10 protocol completers) (20).

The desiccated stigmas of *Crocus sativus* L. flowers are designated as saffron. The principal bioactive constituents of saffron consist of crocin (synthesized through esterification of crocetin with carbohydrate moieties), crocetin, picrocrocin, and safranal (21). The chemical composition of saffron encompasses water, nitrogenous compounds, anthocyanins, glycosides, monoterpenes, aldehydes, flavonoids, vitamins, volatile oils, proteins, amino acids, carbohydrates, minerals, fiber, alongside picrocrocin and apocarotenoids such as crocetin, crocin, and safranal (bio-oxidative derivatives), which represent the most clinically significant bioactive agents.

Picrocrocin confers the characteristic bitter taste of saffron. The intense chromatic properties of saffron derive from crocin, whereas safranal is the primary determinant of its aromatic profile. Picrocrocin comprises 26% of saffron's dry mass. Safranal, a monoterpene aldehyde, is biosynthesized via hydrolysis and dehydration of picrocrocin. Picrocrocin, a water-soluble decarboxylated carotenoid, is enzymatically glycosylated to yield crocin. Crocin—the predominant water-soluble carotenoid in saffron (etymologically derived from the German *krokos*, signifying saffron)—exhibits potent chromogenic activity, producing a vivid crimson pigmentation (22). High-grade saffron typically contains approximately 30% crocin, 5–15% picrocrocin, and approximately 2.5% volatile constituents,

including safranal (23). Crocin, the principal antioxidant in saffron, is a water-soluble carotenoid responsible for its distinctive red coloration (22).

Accumulating evidence indicates that saffron demonstrates therapeutic potential in the management of depression, mediated by its modulation of monoaminergic neurotransmitter systems, including serotonin (5-HT), dopamine (DA), and norepinephrine (NE). The putative mechanism involves competitive inhibition of presynaptic serotonin reuptake transporters (SERT), thereby prolonging synaptic serotonin availability and potentiating its neuromodulatory effects on affective regulation. Randomized controlled trials (RCTs) have established the antidepressant efficacy of saffron as comparable to first-line pharmacotherapies such as fluoxetine (SSRI), imipramine (TCA), and citalopram (SSRI). A systematic meta-analysis concluded that saffron exhibited statistically significant superiority over placebo in ameliorating depressive symptomatology and anxiety indices. Furthermore, its robust antioxidative and anti-inflammatory properties may attenuate oxidative stress and neuroinflammation, which are central pathogenic factors in depressive disorders (21, 23).

To corroborate these findings and establish definitive evidence for saffron's efficacy, safety, and pharmacodynamic mechanisms in major depressive disorder (MDD), large-scale, multicenter, double-blind clinical trials are warranted. Standardization of bioactive constituents and rigorous phytochemical characterization are imperative to ensure reproducibility and facilitate translational applications in clinical practice (22, 23).

Untreated depression may diminish adherence to pharmacotherapeutic regimens, exacerbate the risk of stimulant use relapse, and heighten suicidality. Prior epidemiological investigations have documented elevated rates of depressive symptomatology among individuals with methamphetamine dependence, with one clinical trial specifically screening for major depressive disorder (MDD). Nevertheless, evidence-based interventions for this cohort remain inadequately characterized. This study evaluated the adjunctive therapeutic efficacy of crocin on depression severity during methamphetamine withdrawal in male individuals with substance use disorders (SUDs). SUDs impose a substantial global burden, affecting millions annually (24). Substance dependence and addiction encompass a syndromic array of cognitive, behavioral, and psychological manifestations arising from chronic or dysregulated drug consumption, marked by neuroadaptive hyperexcitability, escalating dosage requirements to maintain homeostatic equilibrium, and consequent physiological dependence (25). Despite the historical prevalence of substance-related pathologies, SUDs have emerged as a pressing transnational public health crisis in recent decades, attributable to rising incidence rates, severe multilevel consequences (individual morbidity/mortality, familial discord, societal economic strain), and the multifactorial etiopathogenesis involving psychosocial, socioeconomic, and geopolitical determinants (15–17).

Per the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5; 5th ed.), substance use disorders are operationalized through 11 diagnostic criteria: (1) consumption exceeding intended parameters, (2) persistent craving, (3) disproportionate time allocation to substance procurement, (4) intense substance-seeking urges, (5) role obligation failures, (6) dose escalation, (7) abandonment of occupational/recreational pursuits, (8) recurrent high-risk use, (9) sustained physical/psychological sequelae, (10) pharmacological tolerance, and (11) withdrawal phenomena (18).

Methamphetamine—a synthetic phenylalkylamine derivative—exhibits divergent neuropharmacological properties from amphetamine, particularly in its pronounced central

nervous system (CNS) stimulation and distinct acute/chronic health ramifications. Methamphetamine ranks among the most prevalent illicit substances globally, paralleling cannabis and opioids in abuse prevalence. Its consumption demonstrates marked endemicity in East and Southeast Asia, with escalating public health concerns in Australia, North America, Central Europe, and South Africa (2). Frequent psychiatric comorbidities among methamphetamine users include attention-deficit/hyperactivity disorder (ADHD), anxiety spectrum disorders, major depression, eating disorders, post-traumatic stress disorder (PTSD), substance-induced psychotic disorders, borderline personality disorder, and antisocial personality disorder (2).

Relapse constitutes a principal challenge in SUD management, occurring in 80% of individuals with substance dependence, with >60% resuming use within 6 months post-cessation (19). Relapse vulnerability is multifactorial, mediated by:

- Endogenous determinants (e.g., affective state, somatic comorbidities).
- Exogenous determinants (e.g., social reinforcement contingencies, socioeconomic stressors) (20).

The neurobiological substrate of relapse involves environmental stressors and psychostimulants inducing glutamatergic activation within the ventral tegmental area (VTA), prefrontal cortical regions, and amygdalar complexes, culminating in dopaminergic efflux from VTA neurons to the nucleus accumbens (NAc). This NAc dopamine release represents the terminal neurochemical correlate of relapse pathogenesis (19).

Herbal therapeutics currently occupy a therapeutically significant niche in addressing psychiatric disorders, including anxiety and depressive syndromes (21). While phytopharmaceutical modalities demonstrate comparatively modest efficacy relative to synthetic agents, their superior tolerability profiles and reduced propensity for pharmacokinetic interactions position them as viable adjuncts (22, 23). Augmentation strategies integrating botanical derivatives with conventional antidepressants show potential in attenuating adverse effect profiles (e.g., tremor, psychomotor agitation) while enhancing cost-efficacy, thereby expanding their utility in depressive disorder management (23, 24). Natural product libraries constitute rich repositories of bioactive phytochemicals with putative neuropsychiatric applications (25).

Accruing clinical evidence substantiates the antidepressant efficacy of *Crocus sativus* (safron) in mild-to-moderate depression. Therapeutic equivalence—or superiority—to imipramine and fluoxetine regimens has been established through standardized metrics such as the Hamilton Depression Rating Scale (HAM-D) (23, 26, 27).

The antidepressant pharmacodynamics of crocin have been empirically validated across preclinical models (3). In a 4-week parallel-group trial conducted at Ebne-Sina Psychiatric Hospital (Mashhad, Iran), 40 major depressive disorder (MDD) patients (age range: 24–50 years) underwent randomization to placebo or active treatment arms. The intervention cohort received fluoxetine (20 mg/day), sertraline (50 mg/day), or citalopram (20 mg/day) co-administered with crocin (30 mg/day). Outcomes suggested crocin-mediated augmentation

of therapeutic response in MDD (1). A subsequent 8-week investigation involving 34 metabolic syndrome (MetS) patients employed double-blind randomization to crocin (30 mg/day; two 15 mg tablets) or placebo. Crocin administration significantly attenuated depressive symptomatology in MetS patients versus placebo controls, with observed effects independent of serum prooxidant-antioxidant balance (PAB) modulation (31).

In a double-blind randomized controlled trial (RCT), 47 burning mouth syndrome (BMS) patients received either citalopram (n=21) or crocin (n=26) over an 11-week intervention period. Longitudinal HAM-D assessments demonstrated crocin's significant amelioration of BMS-associated affective disturbances (5). A separate RCT evaluating methadone-maintained patients during opioid withdrawal protocols revealed that adjunctive crocin (30 mg/day for 8 weeks) significantly enhanced quality-of-life metrics compared to placebo, underscoring its clinical applicability in dependency management (4).

Existing evidence highlights pronounced therapeutic lacunae in managing comorbid major depressive disorder (MDD) and methamphetamine use disorder (MUD). Psychological intervention trials—notably cognitive behavioral therapy (CBT)—remain methodologically constrained, with extant data suggesting efficacy in mitigating methamphetamine dependence but not ameliorating concurrent depressive symptomatology in polysubstance-using cohorts. Pharmacotherapeutic investigations targeting antidepressant efficacy in methamphetamine withdrawal with affective comorbidities have yielded null results (23). Contrastingly, a double-blind randomized controlled trial (RCT) evaluating citicoline (an endogenous phospholipid biosynthesis intermediate) demonstrated modest reductions in depressive severity among adults with unipolar/bipolar depression and concomitant methamphetamine use, though devoid of abstinence-promoting effects (23).

Citicoline, a rate-limiting intermediary in structural phosphatidylcholine synthesis, exerts putative neuroregulatory effects via tyrosine hydroxylase upregulation, thereby augmenting prefrontal catecholamine (dopamine/norepinephrine) bioavailability. Chronic methamphetamine exposure induces mesocorticolimbic dopaminergic circuitry dyshomeostasis; citicoline's capacity to attenuate such neuroadaptations posits a mechanistic basis for mood modulation. A proof-of-concept pilot investigation of modafinil—a non-amphetamine wakefulness-promoting agent—in MUD reported interim depressive symptom improvement, though interpretative caution is mandated given the minuscule completer cohort (n = 4) (24).

A subsequent Phase IIa trial (n = 10 completers) combining modafinil with CBT in HIV-seropositive males evidenced decreased methamphetamine use (via timeline follow-back) and depressive severity (Hamilton Depression Rating Scale) across a 12-week intervention window (25). Modafinil's psychostimulant properties—mediated via dopamine transporter inhibition and orexinergic modulation—may underpin transient thymoleptic effects. Importantly, extant RCTs evaluating adjunctive non-amphetamine psychostimulants or antidepressants in MUD exhibit three cardinal limitations: 1. negligible therapeutic signal, 2. unfavorable adverse event profiles, and 3. recruitment of small, phenotypically homogeneous samples, substantially constraining external validity(26).

These findings highlight the imperative for innovative and enhanced therapeutic strategies in addressing concurrent depression and methamphetamine use disorder (MUD). Thus, until a comprehensive evidence base is established for managing this comorbidity, research efforts must prioritize the design and execution of clinical trials evaluating compounds with dual

therapeutic efficacy. In this context, saffron (*Crocus sativus*)—a botanical agent with established antidepressant properties—emerges as a viable candidate for mitigating depression comorbid with methamphetamine withdrawal.

Preclinical and clinical investigations demonstrate that psychostimulant withdrawal elicits physiological and behavioral responses closely mirroring depressive symptomatology. Notably, withdrawal-induced depressive manifestations peak in severity within the initial 24 hours of abstinence, followed by progressive attenuation over subsequent days. Subclinical depressive symptoms persist for a minimum of three weeks in individuals maintaining methamphetamine abstinence, while anhedonia and subsyndromal depressive features.

remain prevalent even among those sustaining remission for ≥ 2 months. Heightened risks for depressive relapse persist for up to five years post-cessation(9) . Consequently, pharmacotherapeutic management of methamphetamine withdrawal routinely incorporates antidepressant agents to ameliorate these sequelae.

In light of the paucity of prior investigations into crocin's efficacy in ethamphetamine withdrawal-associated depression, this study assessed the adjunctive therapeutic effects of crocin on depressive severity in male methamphetamine users. Favorable outcomes could advocate for the incorporation of crocin into methamphetamine abstinence regimens, thereby attenuating risks concomitant with untreated withdrawal-related depressive states, such as pharmacotherapy nonadherence, stimulant relapse, and suicidality.

Despite substantiated evidence of elevated depression prevalence in methamphetamine-dependent populations, therapeutic modalities for this cohort remain insufficiently delineated. Although recent studies have investigated therapeutic interventions for methamphetamine dependence, the management of comorbid psychiatric manifestations has not been rigorously evaluated. To address this gap, the present study investigated the adjunctive therapeutic potential of crocin on withdrawal-associated depressive severity in male methamphetamine users.

Methods

This triple-blind, randomized, placebo-controlled clinical trial was conducted at the Educational-Research Treatment Center of Ebn-e-Sina Hospital in Mashhad during 2023–2024.

The sample size was calculated using G*Power software, with an alpha error of 0.05 and statistical power of 90%, based on mean Beck Depression Inventory (BDI) score changes reported in a prior study (27). The initial calculation yielded 6 participants per group; however, to accommodate attrition and enhance power, the sample size was increased to 30 participants per group.

Sixty male patients aged 20–50 years, diagnosed with moderate depression secondary to methamphetamine withdrawal, were enrolled via purposive sampling. Eligibility required confirmation of depression severity through psychiatrist-conducted clinical interviews and BDI assessment. Participants were either admitted to or seeking treatment at Ibn Sina Hospital and provided written informed consent prior to enrollment.

The intervention group received 15 mg crocin tablets once daily for 12 weeks, while the control group received visually identical placebo tablets on the same schedule.

Randomization and Allocation.

Simple randomization was implemented using the web-based tool <https://www.Randomization.com> to generate a sequence for allocating 30 participants to each group. Eligible individuals were assigned to the crocin or placebo arm according to the pre-generated sequence until both groups reached full enrollment.

Inclusion and Exclusion Criteria

Inclusion criteria comprised:

- Males aged 20–50 years with moderate depression secondary to methamphetamine withdrawal.
- Willingness to provide informed consent.

Exclusion criteria included:

- Comorbid physical illnesses (e.g., cancer, HIV/AIDS, multiple sclerosis) or psychiatric disorders.
- Documented hypersensitivity to saffron or its derivatives (e.g., crocin).
- Non-adherence to the regimen or crocin-related adverse effects necessitating discontinuation.

Two psychiatrists conducted structured interviews to assess medical history, psychiatric comorbidities, and hypersensitivity to saffron derivatives.

Instruments

Beck Depression Inventory (BDI):

The Beck Depression Inventory (BDI) is a 21-item self-assessment instrument wherein respondents select one of four statements per item, corresponding to graded severity levels of depressive symptomatology. Each item is scored on a 4-point ordinal scale "0–3", culminating in a total score range of 0–63 (28). Depression severity is stratified as follows:

- 0–13: Absent or minimal depression
- 14–19: Mild depression
- 20–28: Moderate depression
- 29–63: Severe depression

General Health Questionnaire (GHQ-28):

The GHQ-28 consists of 28 items partitioned into four distinct 7-item subscales:

- Somatic symptoms (items 1–7)
- Anxiety and insomnia (items 8–14)
- Social dysfunction (items 15–21)
- Depressive symptoms (items 22–28)

Each item offers four response options, scored via two methodologies:

- Binary GHQ scoring: Responses are dichotomized "0, 0, 1, 1", yielding a global score of 0–28.
- Likert-type scoring: Responses are weighted ordinal "0, 1, 2, 3", producing a total score of 0–84.

Lower scores denote superior mental health in both systems. This study employed Likert-type scoring. A subscale score ≤ 6 classifies individuals as "psychologically intact," whereas scores ≥ 7 indicate potential psychopathology (32). Within the depression subscale, severity is categorized as:

- 0–6: Absent or minimal depression
- 7–11: Mild depression

- 12–16: Moderate depression
- 17–21: Severe depression

The Beck Depression Inventory (BDI) and General Health Questionnaire (GHQ-28) were completed at baseline and at weeks 4, 8, and 12 following the initiation of treatment. Sixty male participants (n=60) diagnosed with moderate depression secondary to methamphetamine withdrawal were recruited via targeted sampling at the Educational-Research Treatment Center of Ibn Sina Hospital in Mashhad. Eligibility criteria were verified through structured clinical interviews conducted by psychiatrists and confirmed via BDI scoring. Written informed consent was obtained prior to randomization, with participants allocated to either the crocin (n=30) or placebo (n=30) arm.

The intervention cohort received daily 15 mg crocin tablets for 12 weeks, while the control group received pharmaceutically matched placebo tablets. Both formulations, prepared by the Faculty of Pharmacy, were indistinguishable in appearance and size. Standard pharmacotherapy for depression was maintained across all participants. Baseline demographic characteristics, comorbid conditions, and concurrent medications were systematically recorded using standardized questionnaires.

Depression severity was longitudinally assessed using the BDI and GHQ-28 instruments, both psychometrically validated in Iranian cohorts (29, 30). Assessments were conducted at baseline and weeks 4, 8, and 12 post-interventions. Non-hospitalized participants were scheduled for in-person visits to complete questionnaires; telephone-based assessments were utilized when in-person attendance was not feasible.

To mitigate participant attrition and monitor treatment-emergent adverse events, weekly telephonic follow-ups were implemented. Participants were provided with direct contact details of the study investigators to report any adverse effects, all of which were rigorously documented.

Analyses were performed using SPSS software (version 26), with statistical significance defined as $\alpha=0.05$. Descriptive statistics, including tabular and graphical summaries, were generated to characterize the dataset. Normality assumptions were evaluated using Shapiro-Wilk testing, informing the selection of parametric (independent t-test) or non-parametric (Mann-Whitney U test) methods for between-group comparisons of continuous variables. Categorical variables were analyzed using Pearson's chi-square or Fisher's exact tests. Longitudinal within-group analyses employed repeated-measures ANOVA for normally distributed data, supplemented by non-parametric analogues (Friedman test) where distributional assumptions were violated.

Ethical Considerations

The institutional review board of Mashhad University of Medical Sciences granted ethical approval for the study protocol. Informed consent procedures included explicit disclosure of study objectives, methodologies, and potential risks/benefits. Participant confidentiality was preserved through anonymized data encoding and secure digital archiving. All participants retained the unequivocal right to withdraw from the study without penalty.

Ethical Approval

This study received ethical approval on .../.... /..... from the Institutional Ethics Committee of the Faculty of Medicine at Mashhad University of Medical Sciences. The protocol, registered under the title "Adjunctive Crocin for the Treatment of Withdrawal-Associated Depression in Male Methamphetamine Users: A Randomized Controlled Trial" (approval code: IRCT20160804029191N3), adhered to international ethical guidelines for clinical research

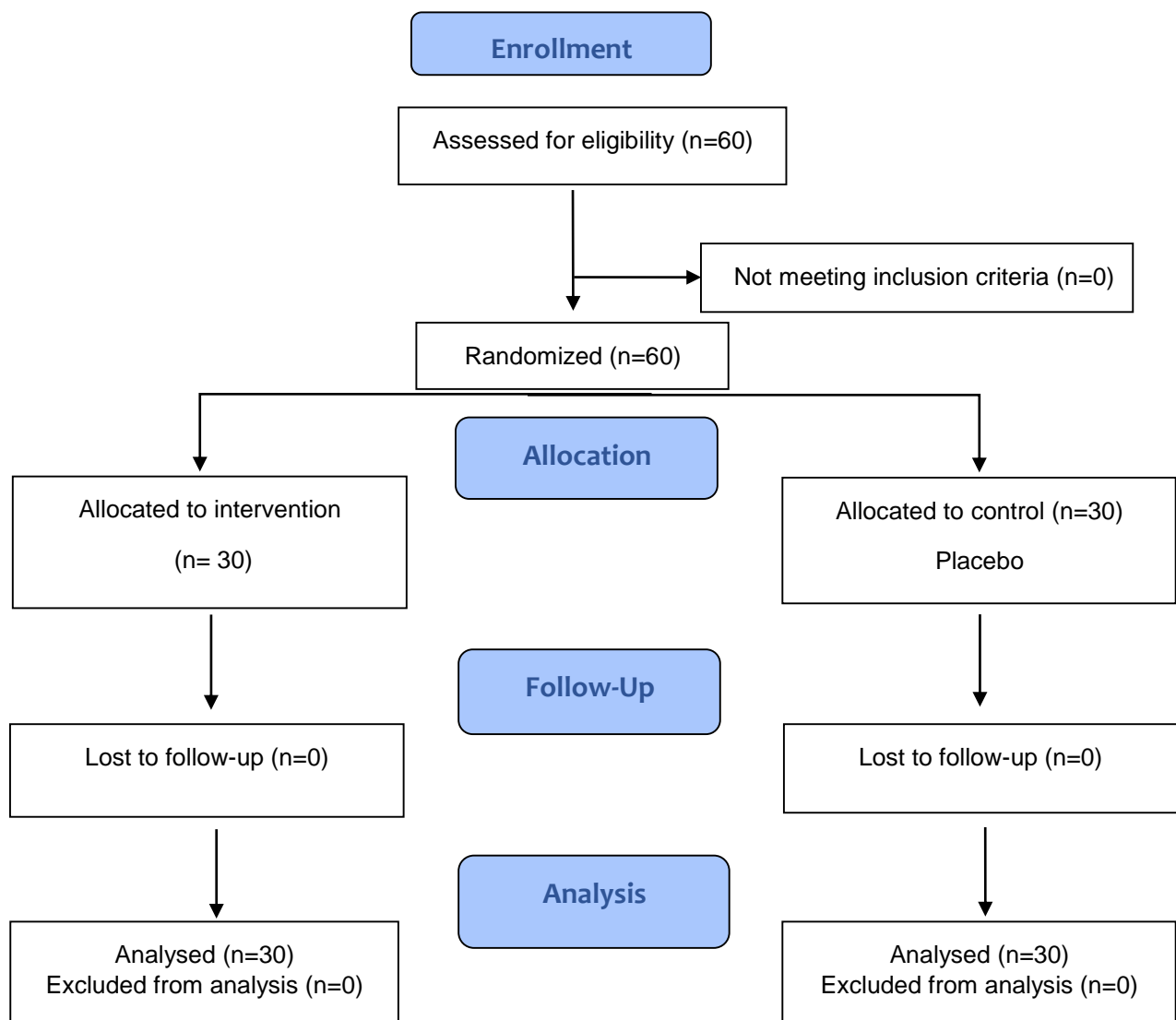


figure1: patient selection and Fallow-up Diagram(CONSORT)

Findings

A total of 60 male patients diagnosed with moderate depression secondary to methamphetamine withdrawal and presenting to Ebn-e-Sina Hospital in Mashhad during years 2023–2024 was enrolled in this study. Participants, comprising individuals with a history of methamphetamine or cannabis use, were randomly allocated into two age-matched groups: a control arm (placebo) and an intervention arm (crocin), each comprising 30 subjects. No attrition occurred during the treatment period, and all participants completed the trial per protocol. No serious adverse events necessitating withdrawal from the study were documented.

The mean age in the placebo group was 37.1 ± 1.25 years, and in the curcumin group, it was 33.0 ± 1.88 years. There was no significant difference in the mean age between the two groups ($p=0.106$).

Analysis of educational attainment revealed a predominance of university-educated individuals in both groups. The distribution of educational levels did not differ significantly between the placebo and crocin groups ($p = 0/546$).

Evaluation of psychiatric comorbidities demonstrated that 66/7% of the placebo group and 76/7% of the crocin group had no documented psychiatric history. Notably, 13/3% of the placebo group and 13/3% of the crocin group reported a documented history of anxiety disorders, whereas 20% of the placebo group and 10% of the crocin group exhibited a prior diagnosis of depression. Comparative analysis revealed no statistically significant intergroup differences in baseline psychiatric comorbidities ($p = 0/603$).

The median (interquartile range [IQR]) duration of depressive symptoms in both the placebo and crocin groups was 2 (2) months, with no significant disparity between the groups ($p = 0/442$).

In both the placebo and crocin groups, 36/7% of participants reported cannabis consumption, whereas 63/3% reported methamphetamine use. No significant intergroup difference was observed in substance distribution ($p = 1/00$).

Baseline mean BDI scores in the placebo and crocin groups were $38/23 \pm 4/73$ and $35/30 \pm 3/34$, respectively. Post-intervention scores declined to $16/60 \pm 4/99$ and $13/10 \pm 3/76$. Within-group reductions across treatment weeks were statistically significant ($p < 0/001$), with between-group differences evident at all-time points ($p < 0/001$). However, longitudinal trajectories of score changes did not differ significantly between groups ($p = 0/160$). figure 1 depicts the longitudinal trajectory of BDI-derived depression scores.

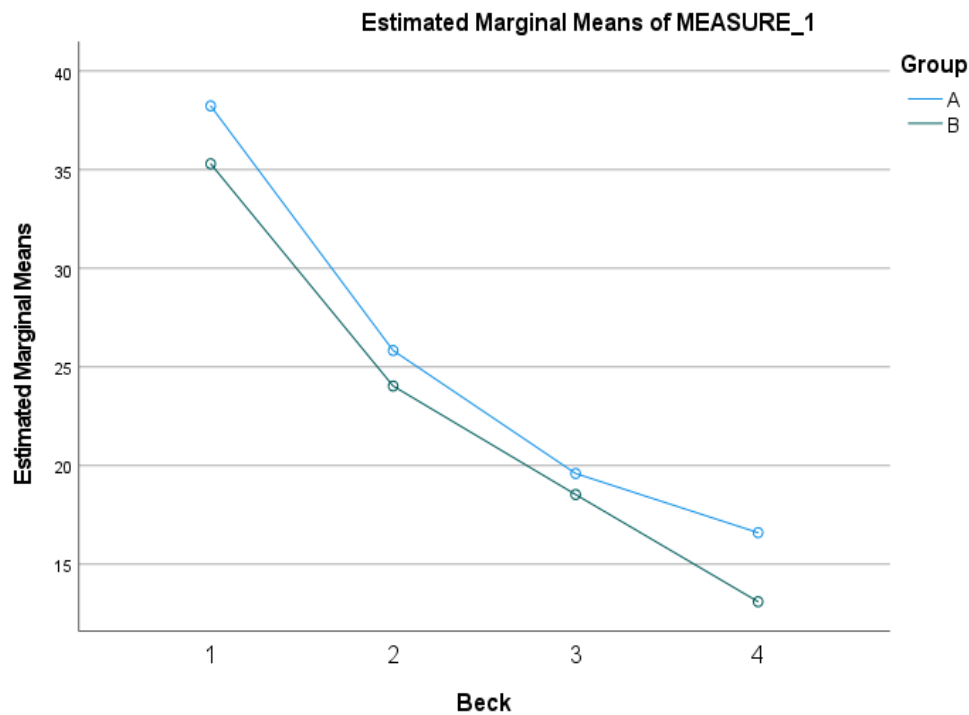
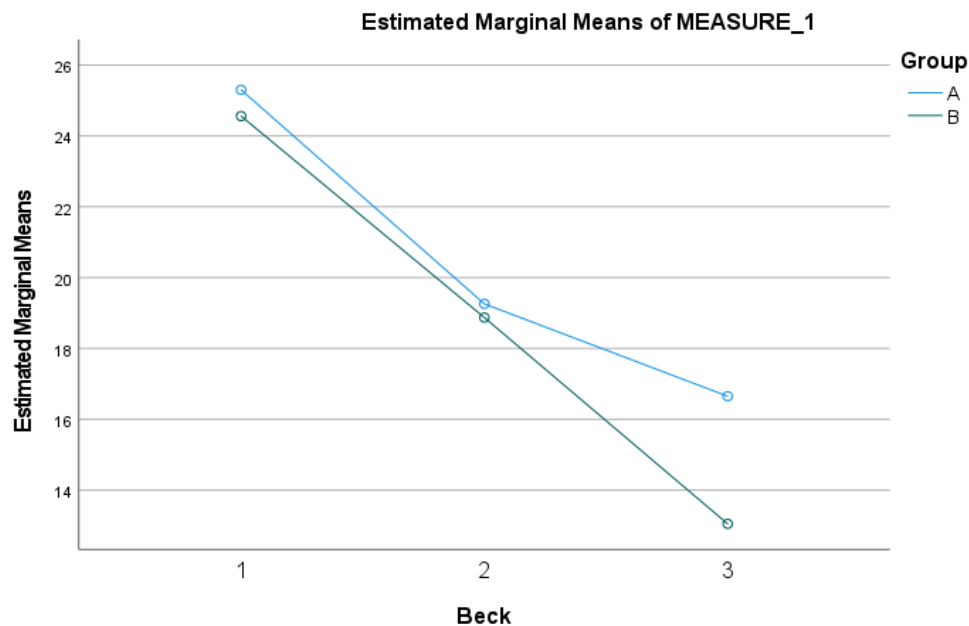


figure 2: Trend of depression scores calculated with the Beck Depression Inventory during different study periods (A: placebo and B: crocin)

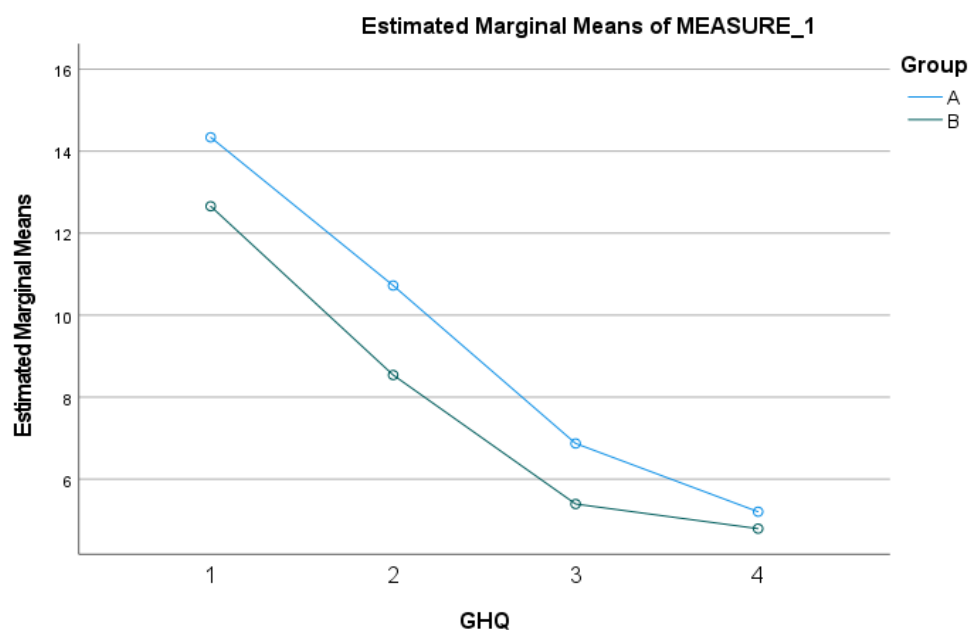
Following adjustment for age and baseline depression severity, the temporal trend of score reduction remained comparable between groups ($p = 0/098$). Figure 2 displays age- and baseline-adjusted BDI scores across study intervals.



Covariates appearing in the model are evaluated at the following values: Beck0 = 36.77 , age = 35.32

Figure 3: Trend of depression scores calculated with the Beck Depression Inventory during different study periods, homogenized for age and pre-intervention scores (A: placebo and B: crocin)

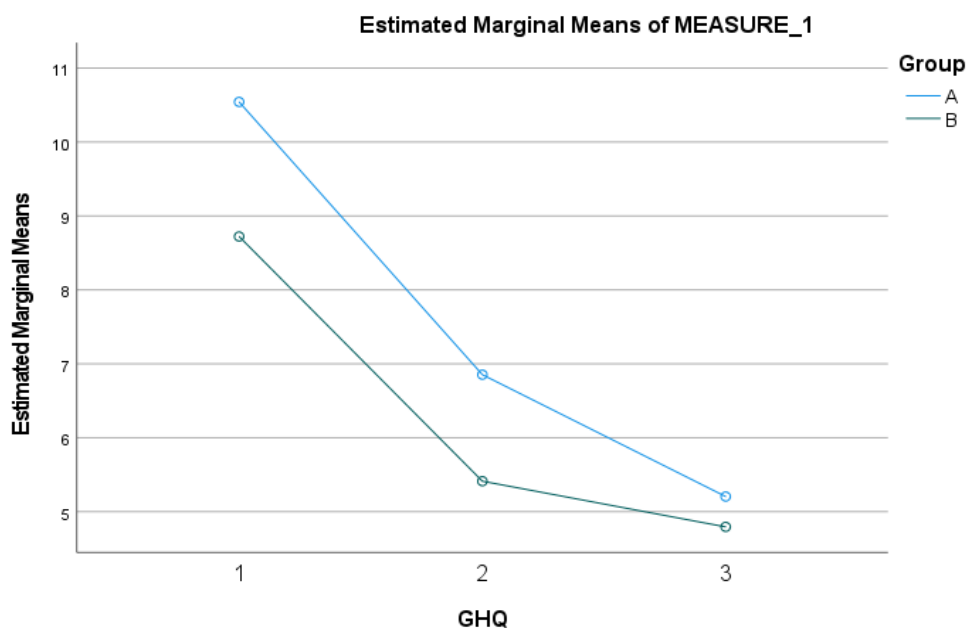
Baseline mean GHQ depression scores in the placebo and crocin groups were $14/10 \pm 4/78$ and $12/90 \pm 4/53$, respectively. Post-intervention scores declined to $5/17 \pm 2/60$ and $4/83 \pm 2/42$. Within-group reductions were statistically significant ($p < 0/001$), and between-group differences emerged across time points ($p = 0/006$). No significant divergence in longitudinal score trajectories was observed ($p = 0/369$). Figure 3 illustrates the temporal progression of GHQ-derived depression scores.



Covariates appearing in the model are evaluated at the following values: age = 35.32

Figure 4: Trend of depression scores calculated with the General Health Questionnaire during different study periods (A: placebo and B: crocin)

After adjustment for age and baseline depression severity, between-group trajectories remained comparable over time ($p = 0/344$). Figure 4 presents age- and baseline-adjusted GHQ depression scores.



Covariates appearing in the model are evaluated at the following values: age = 35.32, GHQ0 = 13.50

Figure 5: Trend of depression scores calculated with the General Health Questionnaire during different study periods, homogenized for age and pre-intervention scores (A: placebo and B: crocin)

These findings suggest that crocin, at the studied dosage, does not confer therapeutic benefit for methamphetamine/cannabis withdrawal-induced depression in males. This aligns with evidence refuting saffron's efficacy in major depressive disorder (31). Contrastingly, trials employing higher crocin doses (30 mg/day for six weeks or 15 mg/day for eight weeks) report clinically meaningful reductions in depression and anxiety (38,47). Beneficial effects of 30 mg/day crocin over eight weeks have also been documented in metabolic syndrome-associated depression (32) and major depressive disorder (27). Among methadone maintenance therapy (MMT) recipients, 30 mg/day crocin for eight weeks reduced depression and anxiety severity (33). Heterogeneity in study outcomes may reflect disparities in disease subtype, substance use profiles, treatment duration, dosage regimens, and psychometric assessment methodologies. Variability in crocin dosing (15–30 mg/day) and treatment duration (4–12 weeks) across trials complicates cross-study comparisons. Pharmacokinetic interactions and genetic polymorphisms in drug metabolism may further contribute to inconsistent findings.

Methamphetamine misuse is characterized by euphoric sensations and mood elevation, while withdrawal manifestations encompass depressive symptoms, fatigue, lethargy, and psychomotor retardation(34) . Consequently, depressive symptomatology may be associated with chronic methamphetamine use and subsequent abstinence (35, 36).

Discussion

In accordance with the study protocol, no participant attrition occurred during the treatment period, and all data were included in the final analysis. No adverse events requiring study discontinuation or resulting in clinically significant complications were documented. Baseline demographic and clinical characteristics—including mean age, educational attainment, psychiatric history, duration of depressive symptoms, and substance type (methamphetamine/cannabis)—were comparable between groups. Analyses demonstrated statistically significant within-group reductions in Beck Depression Inventory (BDI) scores across treatment weeks ($p < 0/001$). However, longitudinal trajectories of score reduction did not differ significantly between groups. Adjustment for age and baseline depression severity similarly revealed no intergroup differences in temporal trends. Comparable patterns were observed for General Health Questionnaire (GHQ) depression scores, with significant within-group reductions ($p < 0/001$) but no between-group divergence in longitudinal trajectories.

Physiotherapeutic agents, notably saffron-derived compounds, have garnered interest as adjunctive therapies for mental health disorders, including depression and anxiety. Accumulating evidence underscores the potential of crocin—a principal bioactive constituent of saffron—to ameliorate depressive and anxiety symptoms in mood disorders, metabolic syndrome, and postpartum depression. Furthermore, crocin supplementation has been associated with improvements in mental health indices and metabolic profiles among patients undergoing methadone maintenance therapy (32, 37, 38). Randomized controlled trials (RCTs) corroborate the efficacy of crocin in reducing BDI and Beck Anxiety Inventory scores relative to placebo (39-41).

The mechanistic basis of crocin's psychotropic effects remains incompletely elucidated; however, its potent antioxidant activity may attenuate oxidative stress and enhance neurocognitive function (42). Preclinical investigations posit that the antidepressant properties of saffron bioactive (crocin and safranal) arise from serotonin reuptake inhibition and modulation of monoaminergic pathways. A rodent model of morphine dependence revealed no reduction in withdrawal-induced depression or anxiety-like behaviors after 10 days of saffron administration, yet significant improvements emerged following 30-day treatment (43). In a 12-week double-blind RCT, patients with major depressive disorder receiving curcumin or combined curcumin/saffron regimens exhibited marked reductions in depressive and anxiety symptomatology (44). Similarly, a 12-week regimen of 50 mg/day saffron yielded superior reductions in depressive and anxiety symptoms compared to placebo (45).

The present trial evaluated crocin's efficacy in mitigating methamphetamine withdrawal-induced depression among male participants. No significant intergroup difference in depressive symptom improvement was observed between the cohort receiving 15 mg/day crocin for 12 weeks and controls. The intervention was well-tolerated, with no adverse effects reported.

A cross-sectional study demonstrated that psychological symptoms, including depression subscale scores, were statistically elevated among individuals reporting escalating methamphetamine use (46). However, the current investigation did not assess methamphetamine dosage in relation to abstinence-induced depressive episodes. Furthermore, a recent study identified methamphetamine-aggravated symptomatology across three domains, with anxiety serving as the principal component of the affective domain (47). Notably, the present study did not evaluate the interplay between anxiety severity and depression secondary to methamphetamine withdrawal. Depressive symptoms exhibit a robust correlation with suicidal ideation and diminished quality of life (48, 49). Concordant with these observations, suicide attempt frequency and severity demonstrate significant associations with depressive symptoms in methamphetamine-dependent individuals (50). Critically, depressive symptoms represent a predominant cluster within the withdrawal syndrome, underscoring the necessity to evaluate confounding variables to substantiate crocin's antidepressant efficacy.

Limitations

The longitudinal assessment of crocin's antidepressant effects in methamphetamine withdrawal patients, protracted treatment duration, and utilization of demographically homogeneous cohorts—stratified by gender, age, educational attainment, and depression-related comorbidities—constituted key methodological strengths. However, critical confounders including methamphetamine dosing patterns (e.g., age of onset, cumulative exposure), socioeconomic determinants, occupational status, and familial support systems were not analyzed. This study did not employ a dose-response framework to evaluate crocin's antidepressant properties. Concurrent psychological parameters such as stress and anxiety, which frequently co-occur with depression in substance withdrawal paradigms, were likewise unexamined. Furthermore, crocin's modulation of inflammatory biomarkers, oxidative stress parameters, and transcriptional activity remained uninvestigated.

Recommendations

The implementation of variable dosing regimens across discrete treatment intervals may refine the translational relevance of these findings and optimize therapeutic protocols for clinical recovery. Longitudinal surveillance of post-treatment evidence could delineate treatment durability and facilitate prophylactic interventions within extended follow-up frameworks to mitigate methamphetamine recidivism. Craving intensity, stress reactivity, anxiety trajectories, and suicidality—cardinal psychological determinants of withdrawal pathophysiology—warrant systematic investigation to elucidate crocin's role in methamphetamine cessation.

Conclusion

In aggregate, daily supplementation with 15 mg crocin over a 12-week interval in patients undergoing methamphetamine/cannabis withdrawal failed to demonstrate clinically significant reductions in depressive symptom severity.

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