Review

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A Prospective Clinical Trial Evaluating a Polyherbal Combination for the Treatment of Opioid Use Disorder

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Abstract

The opioid crisis in the USA affects many people and results in a significant loss of life, degradation of health, and the social fabric. Opioid Use Disorder (OUD) is also a significant motivator for crime, both by opioid users themselves and in the illicit trade supplying them. The trade of illicit opioids is supported by geopolitical rivals of the USA (China) and criminal organizations, and is a significant source of income for criminal and terrorist organizations. It is therefore of vital national interest and national security to end the opioid crisis in the United States on the grounds of both health and national security. This trial protocol presents a means to lower the incidence of OUD, which lowers local crime, healthcare usage, and funding for criminal and terrorist organizations.

Keywords: Opioid use disorder, opioid crisis, illicit trade, addiction, herbal medicine

Introduction

The Opioid crisis is considered one of the most severe health crises in the United States. By 2023-2024, more than 80,000 overdose deaths involved opioids, with most of them being caused by the spread of fentanyl of high purity and other high-strength synthetic opioids. (1) Opioid use disorder (OUD) is an affliction of millions of people and causes chronic relapse, high mortality, and severe comorbidities such as depression, anxiety, and chronic pain. Along with the human cost, the epidemic exerts a massive strain on the emergency departments, addiction-treatment systems, and the infrastructure of public health. (2) According to economic calculations, the overall healthcare, productivity, criminal justice, and mortality expenses of the opioid epidemic in the United States have cost more than 1 trillion dollars every year. (2)

Although there are evidence-based medications to treat opioid use disorder (MOUD), such as methadone, buprenorphine, or naltrexone, many patients still face challenges in terms of the withdrawal severity, lack of symptom management, as well as the inability to adhere to the therapy on a long-term basis. Research has shown that the relapse rates still fall between 60-90% in the first year of withdrawal despite the treatment of the individual. (3,4) Moreover, stigma, scarce access to treatment programs, burden of side effects, and psychosocial stressors also add to treatment discontinuation. These short-

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comings point to the necessity of the non-opioid adjunctive treatment that can help to manage withdrawal, minimize the likelihood of relapse, and focus on biological and psycho-physical mechanisms that are not entirely covered by conventional pharmacotherapy.

There is emerging evidence that nutraceuticals and botanical compounds can have some supportive advantages to the use of conventional OUD treatment. Various natural agents have been shown to exert analgesic, anti-inflammatory, anxiolytic, and neuroregulatory effects applicable to the pathways which are involved in opioid dependence and withdrawal. (5) Some compounds that have been investigated include Crocus sativus (saffron), berberine, Nigella sativa, and Corydalis yanhusuo due to their capability to regulate neurotransmitter systems- especially dopaminergic, serotonergic, and GABAergic pathways- and also affecting cytokine activity, oxidative stress, and neuroadaptations related to chronic opioid exposure. (6,7) Improving preliminary research shows that these compounds can decrease withdrawal symptoms, enhance mood, stabilize sleep, and decrease the intensity of cravings--areas that are closely related to relapse vulnerability.

The recent clinical and preclinical practice also confirms the possibility of the use of nutraceuticals as a part of the OUD treatment models in the form of adjunctive therapies. Saffron components like crocin have shown the effect of decreasing opioid craving and withdrawal scores of patients on methadone treatment. (8) Berberine can inhibit sensitization caused by morphine and has the potential to induce extinction of drug-related behaviour. (9) Nigella sativa supplementation was linked with the alleviation of withdrawal tendency and psychological health. (10) Corydalis alkaloids are modulatory neurotransmitters of analgesia and dopamine, which are relevant to the neurobiology of OUD. (7) Although these agents are not a replacement for normal MOUD, their biological activities imply that they complement the normal MOUD significantly in terms of improved treatment adherence, comfort during the withdrawal process, and long-term recovery outcomes. This accumulating evidence supports the need to conduct systematic clinical trials on nutraceutical combinations as supplements to established OUD therapies.

Demand reduction and routes of exposure

Routes of exposure are divided into unintentional and intentional use. A significant proportion of opioid associated overdoses are due to somebody taking fentanyl-laced recreational drugs. These can be addressed through testing kits being made available at venues where people take recreational drugs, to reduce the possibility of consuming a laced substance.

Opiates are typically consumed through a few routes. Intentional, one-off use of illicit opioids is uncommon, and the majority of illicit opioids are consumed by a small number of addicted persons. For the majority of these cases, they came to use and become dependent on opioids through initial medical use. The challenge of overprescription has been well documented, both in the academic literature as well as in popular media. (11,12) Regulatory approaches aim to stem the non-essential medical use of opiates. (13,14)

Additionally, finding non-addictive alternatives for opioids, (15) or resolving chronic pain (16) will reduce the number of initial encounters to opioids, and reduce the possibility of someone developing opioid use disorder (OUD). For some proportion of the total number of people with OUD, their first exposure is to illicit opioids, and an ecological approach to OUD can help by lowering the availability of opioid products through enforcement, seizures, and border controls.

Some percentage of the illicit opioids in circulation are obtained through direct theft from pharmacies or their suppliers, as well as people misusing their prescriptions. Security on opioids has increased, with many pharmacies not holding opioids on site or locking their opioids in a safe.

Neurobiological Mechanisms and Reinforcing Pathways in Opioid Addiction

Opioid addiction is a chronic relapsing disorder driven by both the acute pharmacological actions of opioids and long-term neurobiological adaptations that promote compulsive use. This section outlines the core mechanisms underlying opioid reward and neuroadaptation, followed by the reinforcing pathways and negative affective states that perpetuate opioid use disorder (OUD).

Neurobiological Mechanisms

Opioids exert their primary effects through activation of μ-opioid receptors (MORs), which are densely expressed in brain regions critical for reward and motivation, including the ventral tegmental area (VTA), nucleus accumbens (NAc), amygdala, and prefrontal cortex. (17,18) Upon activation by agonists such as heroin and prescription opioids,

MORs initiate multiple signaling cascades that have long-term implications for neural function and behavior. These cascades primarily involve inhibition of adenylate cyclase, leading to reduced intracellular cAMP levels and suppression of neuronal excitability and synaptic transmission. This disinhibits dopaminergic neurons in the VTA, increasing dopamine release in the NAc and producing acute euphoric effects. (19,20) Such changes contribute to the reinforcing effects of opioids, reinforcing drug-seeking behavior and habits. (17,20)

Chronic opioid exposure leads to neuroadaptations that modify reward processing circuits, predominantly in the NAc and related areas. These compensatory cellular changes include receptor desensitization, upregulation of cAMP/PKA signaling, and recruitment of β-arrestin pathways. These molecular adaptations engage intracellular cascades such as MAPK/ERK, contributing to long-term synaptic plasticity and changes in gene expression. (17,21) Over time, drug-seeking behavior becomes increasingly habitual, associated with a shift in control from prefrontal cortical circuits to striatal pathways, and impaired regulation of executive function. (18,19)

Reinforcement and Relapse Pathways

Sustained opioid use is maintained through both positive reinforcement (pleasurable effects) and negative reinforcement, in which drug use alleviates the distressing symptoms of withdrawal. These symptoms, such as dysphoria, pain, autonomic dysfunction, and anxiety, arise from hyperactivation of brain stress systems during abstinence. (20,22)

The extended amygdala, including the bed nucleus of the stria terminalis (BNST), becomes increasingly engaged in the withdrawal phase, contributing to heightened negative emotional states. These stress-related circuits involve enhanced signaling via corticotropin-releasing factor (CRF) and dynorphin–κ-opioid receptor (KOR) pathways, which mediate dysphoria and promote relapse as individuals seek to alleviate these feelings through further drug use. (17,20,22)

In parallel, chronic opioid use induces epigenetic modifications, including DNA methylation and histone acetylation changes, which can produce long-lasting modifications in gene expression across brain regions associated with reward and motivation. For example, chronic opioid use can cause DNA methylation changes, affecting genes involved in the addiction pathway, thereby solidifying the maladaptive behaviors typical of opioid dependence. (21,23) These molecular changes may contribute to persistent vulnerability to relapse, even following periods of abstinence.

Importantly, genetic predispositions and environmental stressors interact with these neurobiological mechanisms, influencing individual vulnerability to opioid addiction. (18) This multifactorial nature underscores the challenges in treating OUD and the importance of personalized therapeutic strategies.

Addiction treatment

Once someone has developed opioid dependence, they will continue to seek out opioids to reach an elevated feeling state. In these cases, demand for opioids can be reduced by resolving the physical dependency, as well as the underlying psychological issues. Withdrawal symptom severity is associated with length of use and dosages used in the period of using opioids. (16) Those who use psychotropic drugs, as well as those with a greater propensity for anxiety and depression, were more likely to report severe withdrawal symptoms at the end of a prescription treatment with opioids. (16) Recent opioid use (past 30 days), as well as a cluster C personality disorder, were also predictive of greater withdrawal symptoms. (24) Some genetic variants have been discovered which are associated with rates of OUD, (25,26) as well as severity of withdrawal symptoms. (27,28)

Relapse rates are associated with the severity of withdrawal symptoms. (29) Therefore, through reduction of the withdrawal symptoms, a concomitant increase in opioid cessation success rates can be achieved.

Primary Objective

To establish the efficacy of a co-formulated herbal product (Saffron, Berberine, Nigella sativa, and Corydalis extract) in decreasing opioid withdrawal symptoms in patients with Opioid Use Disorder (OUD), as assessed by the Clinical Opiate Withdrawal Scale (COWS).

Secondary Objectives

- To determine how the herbal combination can impact the frequency of relapse in OUD patients during the research.
- To evaluate the effect of the intervention on patient-reported quality of life and mental well-being, such as anxiety, depression, and the quality of sleep.

- To examine the safety and tolerability of the herbal combination, adverse events, and possible herb-drug interactions.
- To investigate the differences in intervention group and placebo group regarding treatment retention and adherence to outpatient OUD programs.
- To investigate possible neurobiological and physiological indicators of change (e.g., change in mood, craving intensity, or functional capacity), to offer an understanding of mechanisms of action.

Trial Design

A prospective, single-center, case-controlled trial testing for superiority of a combined nutraceutical protocol over a comparator (placebo) group. Each group will consist of 25 individuals with OUD, meeting the inclusion criteria.

Study Setting

The primary care practice of the principal investigator (JV), based in Houston, Texas.

Eligibility Criteria

Patients must have a diagnosed OUD and must be enrolled in an outpatient treatment program for OUD. Additionally, all trial participants must be adults who are of mental capacity sufficient to provide informed consent.

The diagnostic criteria for OUD are defined by the Diagnostic and Statistical Manual, 5th edition (DSM-5), which requires a problematic pattern of opioid use leading to a clinically significant impairment or distress, manifesting in two or more of the following criteria: (30)

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent on activities necessary to obtain opioids, use opioids, or recover from their effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.
10. Tolerance, as defined by either:
    a. A need for markedly increased amounts of opioids to achieve intoxication or the desired effect, or
    b. A markedly diminished effect with continued use of the same amount of an opioid.
11. Withdrawal, as manifested by either:
    a. The characteristic opioid withdrawal syndrome, or
    b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

Severity of OUD is determined by the number of criteria met within the past year:

- Mild: 2–3 criteria
- Moderate: 4–5 criteria
- Severe: 6 or more criteria

Exclusion Criteria

Due to potential safety concerns, the following populations will be excluded from participating in the trial:

- Pregnant women: Saffron can induce uterine contractions and can cause abnormal pregnancy termination. (31)
- Breastfeeding women: Saffron daily dose may be unsafe and high doses may be harmful, particularly when breastfeeding. (32)
- People with bipolar disorder: Saffron has the potential to influence mood and cause excitability in bipolar disorder. (33)
- Individuals with known allergies to saffron, Nigella sativa, or related plant species (Lolium, Olea, Salsola): There have been reports of allergic reactions to saffron, with a cross-reactivity also observed to olive and other species. (33)

- People with bleeding disorders: Nigella sativa (black seed) could alter the coagulation profiles and increase the clotting time. (34)
- People with liver disease or impaired liver function: The safety level of high dosage is not well established; some of the animal studies demonstrate that there is a hepatotoxic potential risk. (35)
- People with high bilirubin levels (hyperbilirubinemia): Investigations into saffron reveal ambiguity in the liver/bilirubin processing during lactation, particularly in neonates. (32)
- People scheduled for surgery (should discontinue use at least two weeks before): Due to the risk of bleeding/coagulation with herbal medicines, including Nigella sativa and saffron, there is a risk with herb-drug/surgery interaction. (36)
- People taking immunosuppressants (e.g., cyclosporine, tacrolimus): Nigella sativa has been shown to influence CYP3A and P-glycoprotein, which inhibits drugs such as cyclosporine. (37)
- People taking anticoagulants or antiplatelet drugs (e.g., clopidogrel): Nigella sativa can be associated with the risk of excess bleeding in case of anticoagulants. (38)
- People taking diuretics (water pills): Nigella sativa exerts diuretic and antihypertensive activity, which might interact with diuretics. (39)
- People taking antihypertensive medications (e.g., amlodipine): Nigella sativa is an antihypertensive drug and can act synergistically. (40)
- People taking serotonergic medications (risk of serotonin syndrome): Nigella sativa has been demonstrated to stimulate serotonin and may cause interaction with serotonergic medications. (38)
- People taking medications metabolized by cytochrome P450 enzymes (due to potential inhibition and drug interactions): Nigella sativa inhibits CYP3A4, CYP2D6, and other CYPs; therefore, it potentiates the risk of herb-drug interaction. (41)
- People with chronic illnesses or those on multiple regular medications (due to risk of interactions): Studies on herb-drug interactions emphasize the need to be cautious when taking more than one medication at a time. (36)
- People with a history of or risk for hepatotoxicity: Hepatic/liver risk was found in animals with extracts of high dosage. (34)
- People with gastrointestinal disorders sensitive to herbal side effects: Nausea, constipation, chronic diarrhea, GERD, and other gastrointestinal disorders are side effects associated with saffron. (42)

Study Design

Our study design is based on a recent study on crocin for OUD, which tests crocin as an adjunct to methadone maintenance therapy. (43)

Outcomes

The COWS score and rate of relapse are the primary outcome variables.

Traditional Pharmaceutical Approach to Opioid Use Disorder

Opioid use disorder occurs in all socioeconomic classes and is associated with increased mortality. OUD affects over 16 million people worldwide and over 2.1 million in the United States, with more than 120,000 deaths worldwide every year. (44) Opioid replacement such as methadone, buprenorphine, and naltrexone are medications that are given to patients with OUD and are widely available through clinics that provide maintenance programs. Maintenance programs are essential in the treatment of OUD. These maintenance programs include psychological support, providing individuals with encouragement and motivation through education, rewarding cooperation, and medications in order to decrease behaviors that perpetuate illicit drug use. (44)

Methadone is a mu receptor agonist that is offered in outpatient monitored clinics. The advantages of methadone treatment include reduced euphoric effects, decreased narcotic cravings, and reduced transmission of infectious diseases through avoidance of intravenous drug use. (44) Methadone treatment in the OUD is safe, and the medication can be tapered according to the patient's progress and dependence. Studies have shown that the use of methadone maintenance may increase patient retention over buprenorphine, additionally, methadone may treat withdrawal symptoms and cravings better than buprenorphine for patients who use fentanyl. (44)

Buprenorphine is a partial mu receptor agonist for which the dosage is gradually increased in order to achieve an effective dose. The medication is used for patients who are in opioid withdrawal. It is im-

perative that the patient is in opioid withdrawal, as buprenorphine can precipitate withdrawal symptoms. Buprenorphine is commonly used in combination with naloxone, a mu receptor antagonist. Naloxone is not absorbed orally and only exerts its action when injected into the bloodstream; the addition of naloxone to the buprenorphine formulation helps reduce opioid abuse. (44) Buprenorphine can be utilized as a subcutaneous solution or may be used as an intradermal implant to aid in long-term maintenance therapy.

Naltrexone is another medication that has been used in the treatment of OUD. (44)

Intervention and rationale

This trial aims to determine the efficacy of herbal medicine in individuals with Opioid Use Disorder (OUD). The interventions include the herbs Saffron, Berberine, Nigella Sativa, and Corydalis extract, and their effects in the treatment of opioid withdrawal and dependence. These herbs were chosen based on their analgesic properties and the evidence these herbs have in the reduction of opioid seeking behavior (Table 1). It has been shown that the use of herbal medication in opioid use disorder has reduced costs (45) and has increased accessibility of these products in patients with OUD. Although these herbs are natural, it is important to evaluate their side effect profile and their potential drug interaction.

Saffron is an herb that is used in food coloring and flavoring and has been shown to have a profound effect on metabolic disorders. (46) The herb has also been shown to be beneficial in patients with cardiovascular disease, obsessive-compulsive disorder (OCD), major depressive disorder (MDD), and Alzheimer's dementia. The effects of saffron in Alzheimer's patients were found to be comparable to the effects of donepezil. (46) Studies have also shown that saffron relieves pain due to its inhibition of prostaglandin release. Nausea, dizziness, headache, and insomnia were associated with saffron use. (46) Hematologic parameters were also studied, and saffron use demonstrated no adverse effects. (47) A prospective case study showed that pregnant women who were exposed to high levels of saffron (over 5 grams), between the first and twentieth weeks of gestation, had significantly higher abortion rates. (47)

Berberine is an isoquinoline alkaloid that has been widely used as an over-the-counter medication for gastrointestinal infections and has also been effective in the reduction of blood glucose levels. (48) Studies have shown that 25 to 50 mg of berberine has been used in the management of opioid use disorder due to its inhibitory properties on morphine-induced sensitization. (48) The herb has the capability to increase neurotransmitters in the brain, such as dopamine, serotonin, and norepinephrine. The herb has also been found to have profound improvements on the cardiovascular system. Cardiovascular disease is one of the leading causes of morbidity and mortality in the United States. Studies indicate that the abnormal proliferation of vascular smooth muscle cells (VSMCs) is involved in the pathogenesis of CVD. (45) Moreover, inflammation has been a key driver in the perpetuation of cardiovascular disease due to its involvement in cardiac remodeling, thus leading to an increase in myocardial oxygen demand and heart failure. Berberine could inhibit angiotensin IV-induced proliferation in cultured VSMCs by targeting the peroxisome proliferator-activated receptor α (PPAR-α)–nitric oxide (NO) signaling pathway. (45) It has also been suggested that 50 mg/kg berberine may improve vascular inflammation and remodeling by inhibiting p38 mitogen-activated protein kinase (MAPK) activation, and activating transcription factor 2 phosphorylation (p-ATF-2) and matrix metalloprotease 2 (MMP-2) expression in rats. (45) Although Berberine is a widely tolerated herb, it is important to evaluate its toxicological implications. At 300 mg of Berberine, the herb has been shown to alter liver transaminases by causing elevation in alanine aminotransferase and aspartate aminotransferase, and has been implicated in causing uterine contraction and may also lead to teratogenic effects. (49) The herb also caused nausea, gastroesophageal reflux disease, diarrhea, and constipation in individuals. (45)

Nigella Sativa is a flowering plant that has been utilized in respiratory, digestive, and cardiovascular diseases due to its anti-inflammatory, anti-viral, and in the reduction of elevated blood glucose levels. It has been widely used to reduce serum lipids, blood glucose levels, increase insulin sensitivity, and improve overall cardiovascular health. A randomized, double-blind, placebo-controlled clinical trial accomplished by Dehkordi FR *et al.* reported a significant reduction of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in a dose-dependent manner in individuals with mild hypertension who were supplemented with 100 and 200 mg of *N. sativa* extract two times daily for 8 weeks. (50) Nigella has been generally well-tolerated. Side effects of the herb included diarrhea, nausea, vomiting, and weight loss. (50) The herb also has implications in drug interactions. Similarly, to Berberine and saf-

fron, Nigella has been found to inhibit cytochrome P450. In addition, *N. sativa* could interact pharmacodynamically with modern antihypertensive medications, as it has reasonable antihypertensive efficacy. (51)

Corydalis extract has been used in traditional Chinese medicine for centuries and has promise in its use in OUD due to the analgesic properties. The herb has the ability to inhibit the dopamine 2 (D2) receptor, thus making it beneficial in the treatment of OUD. (52) Although corydalis has had promising results for the use of OUD, the side effect profile of the herb may be detrimental in individuals. Two case studies showed that after corydalis extract was used, idiosyncratic hepatotoxicity was observed. (52) Following discontinuation of the herbal agent, liver transaminases normalized. Corydalis has also been shown to inhibit cytochrome P450 (CYP450) and UGT. Corydaline was found to be a potent competitive inhibitor of CYP2C19 with *Ki* values of 1.7 μM, indicating that corydaline may be used carefully with drugs metabolized by CYP2C19, such as proton pump inhibitors (lansoprazole and omeprazole), antiepileptics (diazepam and phenytoin), and antidepressants (amitriptyline and imipramine) in order to avoid drug interactions. (53) UGT is another important enzyme needed in the detoxification and degradation of many drugs. In the presence of corydaline, CYP3A-mediated midazolam hydroxylation was decreased with increasing preincubation time in a dose-dependent manner and was also associated with an inhibition of UGT1A9-mediated propofol glucuronidation. (53) This is important when assessing the safety of using Corydalis in combination with other medications because the herb will inhibit the degradation of other drugs, thus increasing the risk for toxicity.

Primary Outcome Measure

Decreased Severity of Opioid Withdrawal

The main finding of this research is the decrease in the severity of opioid withdrawal syndrome, measured by the Clinical Opiate Withdrawal Scale (COWS). The scale is an organized clinical assessment of the severity of withdrawal, which assesses 11 symptoms in the autonomic, gastrointestinal, and neurological areas. Every item is rated to generate a total of 0 to 48 to enable clinicians to categorize the severity of the withdrawal into mild, moderate, and severe withdrawal. (55) The effectiveness of the herbal formulation in reducing withdrawal symptoms will be ascertained by the difference in the total score of the COWS at the baseline and week 12. At least a 25% reduction will be deemed as clinically meaningful. Recent literature places significance on symptom-based monitoring in order to assess the early recovery courses in trials of opioid-use-disorder (OUD). (56,57)

Secondary Outcome Measures

Frequency and Time to Relapse

Relapse will be described as any established incidence of opioid use confirmed with the help of urine toxicology or self-report that is clinician-validated, which meets the modern National Institute on Drug Abuse (NIDA) trial criteria. (58) Analyses will be made on the frequency of relapse and time to the first relapse to evaluate the herbal treatment as a contributor to long-term abstinence and craving management. Recent relapse-following procedures highlight the importance of using both biochemical confirmation and patient self-report in order to be reliable. (59) This outcome will determine the extent to which the formulation minimizes acute withdrawal as well as a prolonged behavioral susceptibility to relapse.

Mental Well-Being and Quality of Life

Validated measures will be used to assess psychological recovery and general well-being at baseline, week 6, and week 12. The Patient Health Questionnaire-9 (PHQ-9) will be used to assess depressive symptoms, (60) the Generalized Anxiety Disorder-7 (GAD-7) will be used to assess anxiety, (61) and the Pittsburgh Sleep Quality Index (PSQI) will be used to assess sleep quality, (62) These were historical instruments that are well-stated and the gold standard when it comes to clinical trials; recent psychometric examination proves that they are structurally valid and reliable with various groups of people. (63,64) As Crocus sativus (saffron) and Nigella sativa are known to have serotonergic and GABAergic modulation effects, and berberine can control dopaminergic activity, better scores on these scales will indicate a neurochemical nature of mood stabilization and sleep. (42,65)

Safety and Tolerability

All the adverse events (AEs) will be reported systematically using the Common Terminology Criteria of Adverse Events v5.0 (CTCAE). (66) The assessment of hepatotoxicity or systemic intolerance parameters will involve baselines and week 12 assessment of hepatotoxicity by biochemical parameters (liver-function tests, bilirubin, renal markers,

and coagulation profile). Bersberis vulgaris and Nigella sativa fall within the category of herbs that have shown a positive safety profile in controlled human trials but could impact hepatic enzymes and serotonergic mechanisms. (67) A five-point Likert scale subjective tolerability questionnaire will be completed by the participants. The results will be used to optimize dosage and safety of herbal OUD regimens in the future.

Mechanistic and Physiological Measures

Craving intensity will be measured weekly through a 0-10 Visual Analog Scale (VAS), (68) and functional recovery will be measured using the WHO Disability Assessment Schedule 2.0 (WHODAS 2.0). (69) Salivary cortisol and β-endorphin assay of a subgroup of participants will be done to examine the modulation of the hypothalamic-pituitary-adrenal (HPA) axis. Recent findings connect the normalization of cortisol rhythm to the lowering of the intensity of cravings and increased self-control in the period of abstinence. (70,71) The links between biochemical indications and clinical outcome will be used to understand the neuroendocrine mechanism of the herbal formulation.

Ethical Considerations

The Institutional Review Board (IRB) of the Independent Medical Alliance in Houston, Texas, will review and approve this trial, and thereafter, the participants may be enrolled. Any study-related activities will be in compliance with the World Health Organization utilization of the Declaration of Helsinki, (72) and the International Council for Harmonization - Good Clinical Practice (ICH-GCP E6 R3). (73) Since this research will be conducted with a vulnerable group of respondents (those receiving opioid use disorder (OUD) treatment), further ethical protections will be provided to guarantee autonomy, ensure a low risk, and foster beneficence. The IRB will review the risk-benefit ratio, plan of data protection, informed-consent documents, and safety measures for the participants. Constant monitoring will be maintained by performing annual follow-up reviews and reporting any adverse events immediately. Human-subjects protection and Good Clinical Practice training will be required for all investigators prior to contacting and working with participants or handling data. (74)

Informed Consent

All prospective participants will be exposed to an informed-consent procedure, which will be carried out by a trained clinician who is competent in the field of addiction treatment. Consent forms will be formulated in simple, non-technical language describing the purpose, the duration, the procedures involved, the potential risks, and the expected benefits of the herbal intervention (Crocus sativus, Nigella sativa, Berberine and Corydalis yanhusuo) provided in addition to methadone maintenance treatment. Other risks, like mild gastrointestinal upset, drowsiness, or interaction with herbs and drugs, will be explained clearly. There will be sufficient time to think about the possibility of participation, discuss it with family, and freely pose questions before signing. Involvement is voluntary, and there will be no consequences for dropping out of accessing methadone or continued medical treatment. Additional understanding tests will establish that consent is informed and voluntary. These protocols follow the existing NIH principles of informed consent in a study involving persons who have been cured of substance addiction. (75,76)

Privacy and Confidentiality

All the phases of the study will be characterized by strict confidentiality standards. Every participant will be given a special code of the study to use instead of personal identifiers on questionnaires, laboratory forms, and biological samples. The personal identifiable information will be kept in a password-protected, encrypted database with restricted access to the principal investigators. The analysis and publication will be done using de-identified datasets. Any physical copy will be locked in hard-filing cabinets in research offices that only a few persons will have access to. The digital files shall be stored in multifactor-authenticated, encrypted institutional servers. Reporting of the data will be done in aggregate form only so that no individual participant can be identified. These steps will guarantee the complete adherence to the Health Insurance Portability and Accountability Act (HIPAA, 2023) and the existing data-governance standards in biomedical research. (77)

Participant Engagement and Retention Strategies

Due to the retention having a significant impact on the data validity of OUD trials, proactive engagement measures will be taken. Reminder calls, texts, and emails will be sent to the participants prior to every visit. Appointment scheduling will be flexible with such schedules as weekend and evening schedules to meet the employment or family demands.

Non-judgmental supportive communication will be upheld by the research staff during the entire participation to establish trust and minimize dropout. Payments are designed to encourage continued involvement and not by force. Participants will receive an invitation to follow-up assessments even after stopping the herbal treatment to ensure that they can perform intention-to-treat analyses. The monthly retention audit will reveal the obstacles and inform the adaptive retention strategies according to the current behavioral-trial standards. (78)

Adverse Event Surveillance and Safety Supervision

All adverse events (AEs) will be constantly tracked and classified according to the Common Terminology Criteria of Adverse Events (CTCAE v5.0). The investigators will record the onset, duration, severity, and potential association with the intervention. Serious or unexpected events will be reported to the IRB and the sponsor of the study within a period of 24 hours. Close monitoring will be done due to hepatic or serotonergic side effects because of the pharmacological nature of the herbal combination. AE summaries will be reviewed by a Data and Safety Monitoring Committee, which will include clinicians and pharmacologists who will give recommendations every two months. Such measures are to comply with the modern expectations of the FDA and ICH regarding safety reporting. (79)

Recruitment

Study recruitment will be performed by flyers provided to methadone outpatient clinics. Patients may ask about the trial to their attending physician, who can provide further information and assess the patient's eligibility. The patient will be directed to fill out a questionnaire, which records basic demographic details, as well as information about their opioid use history. (80) The date of their last opioid use will also be recorded, as long as their Clinical opiate Withdrawal Scale (COWS) score, assessing the severity of their withdrawal symptoms. (81)

Data Collection and Data Management

The trained clinical personnel will be able to collect the data at three times: at the baseline, week 6, and week 12. The scales to be used to measure withdrawal symptoms will be the Clinical Opiate Withdrawal Scale (COWS); mental-health and sleep outcomes will be measured using the PHQ-9, GAD-7, and PSQI; and craving intensity will be measured using a Visual Analog scale of 0-10. Laboratory results will involve hepatic function, serum cortisol test, and β-endorphin test. Data will be directly keyed into an encrypted EDC system that has two-entry validation as well as automated range checks. The samples of blood and saliva will be coded with IDs and kept at -80 °C in safe freezers. Completeness and accuracy will be ensured through weekly audits and monthly reviews of the principal investigator. Exported datasets will only be de-identified to undergo statistical analysis. These steps are in line with the ICH-GCP E6 (R3) standards and the latest best practices with regard to biomedical data governance.

Statistical Methods

All statistical tests will be two-tailed except where a one-sided hypothesis has been explicitly shown to be justified by previous evidence or pharmacologic consideration. The comparison between the intervention and the placebo groups will be done through independent-samples t-tests or analysis of variance (ANOVA) to compare continuous outcomes, including Clinical Opiate Withdrawal Scale (COWS) scores, mental-health indices (PHQ-9, GAD-7, PSQI), and biochemical markers (cortisol and β-endorphin).

In the repeated measurements of the baseline, week 6, and week 12, linear mixed-effects models (LMM) will be used to identify intrasubjective correlations and time variations. Repeated-measures ANOVA with Greenhouse-Geisser correction will be employed when the assumption of sphericity has been violated. The presence or absence of relapses or adverse events is a dichotomous outcome that is analyzed by means of chi-square or Fisher tests. Time-to-event events (e.g., time to first relapse) will be assessed through Kaplan-Meier analysis of survival and will be compared using the log-rank test. The tests of normality and homoscedasticity will be evaluated before the use of inferential tests, and non-parametric analogs (Mann-Whitney U or Wilcoxon signed-rank) will be applied in the cases when the conditions are not met.

To reduce inflation of Type I error between different endpoints, the Bonferroni correction will be utilized in key outcomes (withdrawal severity and relapse frequency), where the family-wise error rate will be 0.05. In the case of secondary and exploratory outcomes such as anxiety, depression, and biomarker levels, the Benjamini-Hochberg false discovery rate (FDR) adjustment will be utilized to balance statistical power and false positive control. Mixed corrections make sure that the multiplicity is strictly con-

trolled, though in a conservative yet efficient way in terms of behavioral, biochemical, and psychological realms. (82,83)

Elimination of potential confounders like age, sex, baseline dose of methadone, years of opioid use, and comorbid psychiatric illnesses will be done through general linear models (GLMs) and multivariate mixed-effects regression. These will be models that will accommodate both continuous and categorical covariates. Subgroup effects will be investigated through stratified analyses, particularly based on sex (because of hormonal differences in cortisol reactions) and age (because of the differences in withdrawal resilience). Sensitivity tests will also be used to evaluate the robustness by eliminating outliers or study members with protocol deviations. Multicollinearity will be checked with the help of variance-inflation factors (VIF < 5 is an acceptable value).

The determination of the sample size is the detection of a moderate effect of the primary outcome (COWS). A sample size of 100 randomized 1:1 to herbal and placebo will have a power of around 85-90 at = 0.05 with an estimated Cohen's d = 0.45 (similar herbal-adjunct OUD studies have achieved this power level with a sample size of 100 participants, e.g., (84). The use of repeated measures at three time points additionally improves power (> 95 percent) as a result of within-subject correlation. The calculations of power are based on the following formula:

$$n = \frac{2\,(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2\sigma^2}{\Delta^2}$$

Where: β = desired power, Δ = expected difference between groups, σ = standard deviation.

Since there are no published RCTs of herbal adjuncts in OUD that have generated an effect size of relapse, the effect size of d = 0.30 is assumed based on existing studies of relapse risk reduction. (85,86)

The missing data will be addressed using multiple imputation by chained equations (MICE), (87) assuming that the missingness is missing at random (MAR). The imputation model will contain auxiliary variables that are predictive of missingness (e.g., baseline severity, attendance). Robustness will be checked using sensitivity analyses based on complete-case and the last-observation-carried-forward (LOCF) approaches. (88) All statistical calculations will be done with R (v4.3.2), IBM SPSS (v29), and Python (v3.11). Both ggplot2 and Matplotlib will be used to create graphical visualizations (e.g., forest plots, survival curves). The GPower (v3.1) will be used to perform power analyses, which will be confirmed by simulation.

Discussion

The analytical framework of the current trial will combine powerful longitudinal modelling methods and validated measurement instruments, which enhances the ability to identify clinically significant impacts of the herbal adjunct treatment of opioid use disorder (OUD). The Clinical Opiate Withdrawal Scale (COWS) is the main outcome measure as it has a large acceptance and validation in both inpatient and outpatient opioid withdrawal cases. (89) Linear mixed-effects models to capture change across a series of time points (baseline, mid-point, endpoint) overcome intra-participant correlation and are more sensitive as compared to simple cross-sectional analyses. Moreover, multiple correction of comparisons through Bonferroni and Benjamini-Hochberg techniques is used to ensure that Type I error is controlled in case of multiple outcome domains.

Frequency of relapse is one of the most difficult endpoints in the OUD research, partly because of the heterogeneity of definitions, follow-up time, and cohort. Most recent trials suggest that the relapse is still prevalent, which supports the idea of OUD being chronic and relapsing. In this regard, it is wise to adopt a conservative effect size assumption (e.g., Cohen d = 0.30) in the estimation of sample sizes due to the scanty intervention-specific effect-size research in herbal adjuncts of OUD. Simultaneously, recent trials of light and circadian interventions support the estimates of the sleep quality and the domain of circadian outcomes; a 2023 meta-analysis showed the improvement of self-reported quality of sleep as measured using the Pittsburgh Sleep Quality Index (PSQI) with a standardized mean difference of −0.72 (95 % CI −1.24 to −0.21). (90)

The exploration of multiple mechanistic outcomes (neuroendocrine biomarkers, sleep, mood) versus enough statistical power has been resolved through the construction of the trial with repeated measurements and relevant power analysis. Altogether, the statistical tools are consistent with the best practice in the complex behavioral-biomedical trials and facilitate the efficacy estimates and the mechanistic inferences.

Conclusion

Overall, this trial has a strong statistical and methodological design that aims at exploring the effectiveness of a herbal adjunct in methadone-assisted recovery of OUD. Using a combination of validated (COWS and PSQI) instruments, mixed-effects modelling, and conservative but informed assumptions about effect sizes, the analysis will then lead to credible and replicable findings that can help inform future integrative approaches to treatment. The conclusions are strengthened by the use of ethical and methodological protection, such as multiple corrections of comparison, sensitivity analysis of missing data, and stratified subgroup analysis. In the event that the intervention proves to be of considerable value, the findings can be extended to increase the adjunctive treatment choices of people with OUD and to justify its implementation in clinical practice.

Table 1. Evidence of Herbs Used to Treat Opioid Use Disorder

Herb	Dosage	Duration	Clinical Rationale	Adverse Effects
Saffron	100 mg 2 capsules BID	12 weeks	Management of opiate withdrawal shows a reduction in patients seeking opiates	Nausea, dizziness, headache, and insomnia at 200 mg (47)
Berberine	100 mg 2 capsules BID	12 weeks	Herbal treatments lower the cost and expand accessibility in patients with OUD	At 100-200 mg nausea, gastroesophageal reflux disease, diarrhea, constipation (48) CYP450 inhibition at 300 mg
Nigella Sativa	100 mg 2 capsules BID	12 weeks	Herbal medicine may lower the degree of withdrawal symptoms, which often cause individuals with OUD to seek opioids, repeating the cycle of addiction (54) N. Sativa has been used in respiratory, digestive, and cardiovascular diseases due to their anti- inflammatory, anti- viral, and hypoglycemic properties (50)	Diarrhea, nausea, vomiting, weight loss (50) Cytochrome P450 inhibition
Corydalis extract	100 mg 2 capsules BID	12 weeks	Efficacy demonstrated by herbal medicines is a basis for their further study and evaluation for possible incorporation into opiate treatment regimens. Corydalis has been used in Chinese medicine for its analgesic properties and neuropathic pain by inhibiting the dopamine D2 receptor, suggesting that it may aid in OUD (52)	Sedative, anxiolytic, antidepressant effects (52) Hepatotoxicity Inhibition of CYP450

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