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REVIEW ARTICLE

Therapeutic Potential of Herbalism for Opioid Use Disorder

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RESUMEN

Introducción: la crisis de los opioides cobra muchas vidas, aproximadamente cien mil al año en Estados Unidos de América, lo que motiva la búsqueda de soluciones. Actualmente, estas se centran en los opioides sintéticos, y son útiles en algunas circunstancias, pero su adopción no ha frenado las muertes por opioides. Existen posibles soluciones para el trastorno por consumo de opiáceos en sustancias conocidas de la medicina herbolaria, y éstas pueden ser opciones de tratamiento atractivas.**Objetivo:** esta revisión tiene como objetivo proporcionar una visión global de las terapias integradoras disponibles para los usuarios actuales de opiáceos para ayudar en el abandono del consumo a través de la disminución de los síntomas de abstinencia. Identificamos varias terapias a base de hierbas y nutracéuticas que requieren una mayor investigación por su potencial terapéutico en el trastorno por consumo de opiáceos. **Método:** realizamos una búsqueda bibliográfica utilizando tres bases de datos: *Google Scholar, China/Asia On Demand y China National Knowledge Infrastructure*. Se diseñó un protocolo que incorpora los lineamientos PRISMA, el cual fue aplicado durante las etapas de búsqueda y selección de artículos. **Discusión y conclusiones:** varios tratamientos a base de hierbas y nutracéuticos, incluidos los extractos de *Sophora alopecuroides*, crocina y *Berberis vulgaris,* y las formulaciones de Hab-o-shefa, Tai-Kang Ning y Fu-Yuan Pellet, resultan prometedores para el tratamiento de opiáceos, lo que motiva su estudio adicional en ensayos a mayor escala. Si se mantienen los resultados de los ensayos previos a menor escala, las hierbas medicinales pueden funcionar como una terapéutica eficaz como parte de un régimen para dejar los opiáceos

Palabras clave: crisis de opiáceos, tratamiento con ibogaína, recuperación de adicciones, medicina herbolaria, trastorno por uso de sustancias.

ABSTRACT

Introduction: the opioid crisis continues to claim many lives, approximately one hundred thousand annually in the United States of America, motivating solutions. Currently, these focus on synthetic opioids and are helpful in some circumstances, but their adoption has not stymied opioid deaths. Possible solutions for opioid use disorder exist in substances known to herbal medicine, and these may be attractive treatment options.**Objective:**: this review aims to provide a comprehensive overview of the integrative therapies available to current opioid users to help in the cessation, through decreasing withdrawal symptoms. We identified several herbal and nutraceutical therapies which require further investigation for their therapeutic potential in opioid use disorder. **Method:** we performed a literature search using three databases: *Google Scholar, China/Asia on Demand, and China National Knowledge Infrastructure*. A protocol was designed that incorporates the PRISMA guidelines, which was applied during the stages of searching and selecting articles. **Discussion and conclusions:** tseveral herbal and nutraceutical treatments, including *Sophora alopecuroides*, crocin, and *Berberis vulgaris* extracts, and Hab-o-shefa, Tai-Kang Ning, and Fu-Yuan Pellet formulations, demonstrate promise for the treatment of opioid use disorder, motivating their further study in larger scale trials. If the results from previous smaller trials hold, herbal medicines may function as effective therapeutics as part of an opiate cessation regimen.

Keywords: opioid crisis, ibogaine treatment, addiction recovery, herbal medicine, substance use disorder.

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INTRODUCTION

Since the first trial of oxycontin, finished in 1994, the patent for the drug has been extended many times through minor modifications, including the addition of a nominally tamper proof coating which prevented the contents from being crushed and snorted.

Purdue Pharma, of which oxycontin was its most significant source of revenue, had cumulative revenues in 2017 of $35 billion USD (Keefe, 2017). Opioids are used by roughly one in 25 American adults (Compton & Volkow, 2006; Von Korff et al., 2008), and 5.7 million Americans met the definition for opioid use disorder (OUD) in the year 2023 (Substance Abuse and Mental Health Services Administration, 2024). There has been an exponential rise in the consumption of opioids: three tons of oxycodone were consumed globally in 1990, rising to 77 tons by 2009, 81% of which was consumed by Americans, who then comprise just five percent of the world's population (Kenan et al., 2012).

Between the years 2013 and 2019, the age-adjusted rate of deaths from synthetic opioids, not including methadone, increased 1040% (Mattson, 2021). There were 70,630 overdose deaths in the USA in 2019, of which 49,860 (71%) involved opioids (Mattson, 2021). OUD, once it has manifested, still has several treatment options available. Addiction can extend for many years; in one survey of court-involved patients, while not representative of the OUD population, more than half (55%) of those surveyed had more than ten years of illicit drug use (Li et al., 2020).

Treatment with ibogaine, an indole alkaloid, for the treatment of physical withdrawal symptoms has shown efficacy in case reports and small trials, and ayahuasca, a plant mixture originally from the Amazon basin containing indole alkaloids, also has supportive evidence for this role (Arenson et al., 2024). State-of-the-art of OUD treatment has typically been methadone-based, and buprenorphine has been recently adopted for the treatment of OUD.

Success rates at treating OUD have historically been low, ranging from 20% to 23% without medication (Eastwood et al., 2017; Krupitsky et al., 2011). Several pharmaceuticals can increase the success rates of treatment for OUD, for example, one trial observed an increase in opiate abstinence with naltrexone treatment from 35% (95% confidence interval: 11%-64%) in the control group to 90% (95% CI: 70%-92%) in the group receiving naltrexone (Krupitsky et al., 2011). In the USA, Suboxone®, a combination of buprenorphine and methadone, is commonly used for OUD (Burma et al., 2017; Lekas, 2014). In China, the pharmaceuticals lofexidine and clonidine are commonly used (Tang et al., 2006), and demonstrate efficacy in treating OUD (Pergolizzi et al., 2019).

This review aims to evaluate the potential of herbal medicines as treatment for OUD. We seek to clarify how herbal medicines can contribute to addressing the opioid crisis in the U.S., especially as cost can be a barrier to treatment initiation (Hall et al., 2021). This review aims to address how herbal medicines including iboga and ibogaine, products from the African Apocynaceae species *Tabernanthe iboga*, can be used as part of a treatment program for OUD, and the comparison on dimensions of cost, accessibility, efficacy and mechanisms of action with standard treatment of OUD with the agents methadone, buprenorphine and/or naloxone, either individually or in combination.

METHOD

Design

We perform a literature search using three databases: Google Scholar, China/Asia on Demand (CAOD), and China National Knowledge Infrastructure (CNKI) for herbal treatments for Opioid use disorder. The treatments must be herbal or nutraceutical, not pharmaceutical or manual. Meta-analyses are included. Studies are evaluated based on the Cochrane ROB2 analysis (Sterne et al., 2019). We include our Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) diagram below (Figure 1), made using the PRISMA 2020 tool (Haddaway et al., 2022).

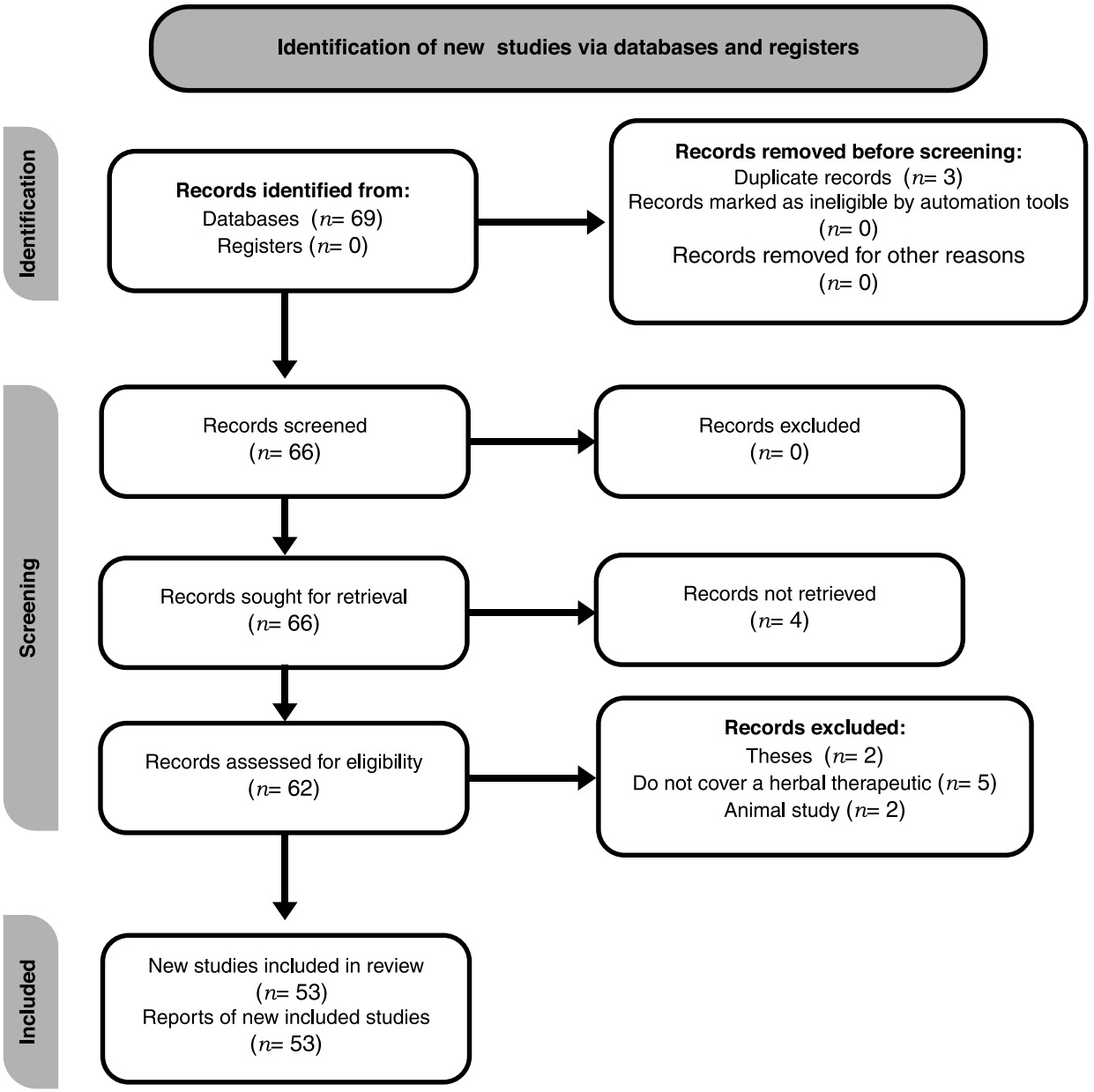
Procedure

This research set out to find natural substances for the treatment of opioid use disorder, aiming to find those tested in clinical trials for an effect on withdrawal symptoms.

For the search of the CAOD and CNKI databases, we used the possible combinations of "Opioid", "Opiate", or "Heroin" for the first time with "Withdrawal", "Dependence", "Cessation", or "Addiction" as the second term. As Google Scholar has a much broader selection of literature, we searched for "Herbal treatments for opioid withdrawal", without quotation marks.

Figure 1

A PRISMA flow diagram for the records included in this review



RESULTS

Withdrawal in Opioid Use Disorder

Withdrawal symptoms are a feature of long term OUD and are a challenge for patients to overcome when embarking on a program of opioid use cessation (Kosten & Baxter, 2019; Pergolizzi et al., 2020).

Management of opiate withdrawal symptoms can result in a greater rate of opiate discontinuation for patients seeking cessation (Pergolizzi et al., 2020).

Opioid withdrawal symptoms can be present even after a single exposure in humans (Jones, 1980), and increase in severity with repeat opiate use (Kenny et al., 2006). Several brain regions and neurological systems are altered by opiate exposure and play roles in opiate withdrawal (Monroe & Radke, 2023), including the mesolimbic dopamine system (García-Pérez et al., 2015), the basolateral amygdala (Deji et al., 2022), the central amygdala (Cabral et al., 2009),

the bed nucleus of the stria terminalis (Song et al., 2020), adrenal stress hormones (Navarro-Zaragoza et al., 2021), locus coruleus (Maldonado et al., 1992), and the periaqueductal gray matter (Maldonado et al., 1992).

Current therapeutics work on the endogenous opioid receptors. The therapeutic buprenorphine is a partial agonist of mu-opioid receptors and naloxone is a partial antagonist of the mu-, kappa-, and delta-opioid receptors. This therapeutic combination, under the tradename of Suboxone®, demonstrates several advantages over methadone for curbing opioid withdrawal (Burma et al., 2017; Lekas, 2014).

Established treatment protocols previously relied heavily on methadone, which acts as a substitute for opiates, having a similar mechanism of action as morphine and producing similar effects (Johnson et al., 2003). Antagonistic therapies, such as naltrexone, do not produce opioid-like effects, instead blocking the effects of opioids should opioids be administered (Johnson et al., 2003).

Alternative Treatment Options for OUD

Non-pharmaceutical treatment options are limited, owing in part to the primacy of Suboxone® treatment. Recently, iboga *(Tabernanthe iboga)*, and the compound ibogaine, have attracted attention for the treatment of OUD (Arenson et al., 2024). Ibogaine may be an effective treatment for OUD as it demonstrates substantive effects on opioid withdrawal symptoms (Brown & Alper, 2018; Mash, 2018). Other herbal medicines, including *Nigella sativa* (Sangi et al., 2008), chamomile (Momeni et al., 2018), ajwain (Momeni et al., 2018) *Sophora alopecuroides* (Hashem-Dabaghian & Kianbakht, 2023; Kianbakht et al., 2020), Datura (Moosavyzadeh et al., 2020; Nazari et al., 2013), *Zataria multiflora* (Sayyah et al., 2017), Fu-Yuan Pellet (Wang et al., 2009), Tai-Kang Ning (Kang et al., 2008), Weini-Com (Hao & Zhao, 2000) and Berberine (Dabaghzadeh et al., 2021), show therapeutic potential in treating OUD.

Ibogaine is currently regarded as a Schedule I drug by the Controlled Substances Act, which specifies that it has high potential for abuse, and no accepted medical uses (The Controlled Substances Act, 1978). Iboga has centuries of use in traditional ceremonies of the Bwiti people in Gabon (Fernandez, 1982). With regards to OUD, ibogaine, the active component of iboga, works as a partial agonist of the mu and kappa opioid receptors, making its mechanism of action more similar to methadone than buprenorphine (Glick & Maisonneuve, 1998). It may work through other mechanisms, including the serotonergic and dopaminergic systems (Govender et al., 2024).

Some caution is required, as between 1990 and 2008 there were nineteen deaths temporally associated with taking ibogaine, an indole alkaloid extracted from the iboga plant, and likely more outside of the published literature (Alper et al., 2012). However, in 12 of the 14 deaths for which there was adequate data, there were either pre-existing comorbidities or recent consumption of commonly abused substances, and these could have been prevented with pre-treatment screening (Alper et al., 2012). Still, many people are motivated to take iboga to treat their substance use disorders (Rodríguez-Cano et al., 2022) despite risks.

Many people have had a continuation of their addictive tendencies even after the physical withdrawal symptoms have been blunted, if not eliminated. Here, cognitive approaches may be important, and psychological support also helpful for ending substance use disorders (SUDs); (Jhanjee, 2014).

Other Herbal Treatments

So far, there is minimal research on other herbal factors which can influence OUD, and several helpful reviews have shared the possibility for herbal medicines in OUD (Bawa et al., 2019; Doosti et al., 2013; Ebrahimie et al., 2015; Kruszecki et al., 2021; Liu et al., 2009; Tabatabai et al., 2013; Ward et al., 2011; Zhu et al., 2017). The agents explored in human studies found through our literature search are included in Supplementary Table 1. Several of these substances are effective at decreasing withdrawal symptoms in OUD, and may be useful in a clinical context, as withdrawal symptoms are a major factor in relapse (Kosten & Baxter, 2019).

The efficacy demonstrated by multiple herbal options is a basis for their further study and possible incorporation into opiate treatment regimes. Possibly, they may be used additively with Suboxone® treatment to lower withdrawal symptoms further, or to taper off from Suboxone® treatment, as buprenorphine has potential for abuse (Chilcoat et al., 2019).

Herbal treatments may also lower the cost of treatment and thereby expand accessibility. If clinical results hold up in larger scale trials and real world settings, simple treatments like berberine and Nigella sativa may be adequate treatments available at low cost. These may help to additionally lower the degree of withdrawal symptoms, which often cause the person with OUD to seek opioids again, repeating the cycle of addiction (Pergolizzi et al., 2020).

Together, iboga and ibogaine (as well as various

herbal remedies included in Supplementary Table 1) may be useful in treating opiate withdrawal symptoms to help treating OUD. The treatments with the greatest evidence for efficacy are the extracts of crocin (Abbaszadeh-Mashkani et al., 2021), Sophora alopecuroides (Hashem-Dabaghian & Kianbakht, 2023; Kianbakht et al., 2020), and Berberis vulgaris extracts (Dabaghzadeh et al., 2021) and Hab-o-shefa (Moosavyzadeh et al., 2020; Nazari et al., 2013), Tai-Kang Ning (Kang et al., 2008; Li et al., 2007), and Fu-Yuan Pellet (Wang et al., 2009) formulations. Evidentiary quality evaluated by the Cochrane RoB2 tool is included for studies in Supplementary Table 1.

Cost and Accessibility

Cost of treatment can hamper accessibility, and low availability of treatment centers is often a barrier for people in need of care for OUD. Trends show increases in the accessibility of centers offering medication treatment for OUD (Cantor et al., 2021). In 2020, 45% of US counties had a facility offering some form of medication treatment for OUD (Cantor et al., 2021). However, even given the expanded coverage, logistical barriers to care still remain, including lack of insurance coverage, a lack of prescribers, low accessibility of treatment, and geographic distance from a treatment center (Hall et al., 2021).

The advantage of the herbal medicines is that they are non-proprietary, and have much lower costs than their patented and synthesized pharmaceutical counterparts. For the purposes of determining accessibility, there are three classes present in the literature: single agents, formulations/combinations, or medical devices. In our case, the medical device studied (Yu & Guo, 2013) was a bespoke system for the experiment, and would have extremely low accessibility. Single agents are divided further based on their accessibility: high accessibility items are available through major retailers, while medium accessibility can be found through more specialty retailers, and low accessibility items have limited availability as products (Supplementary Table 1).

DISCUSSION AND CONCLUSIONS

The opioid crisis is significant motivation to examine non-mainstream treatments for substance use disorders. Given the severity of the crisis, it may be warranted to look outside standard medical curricula to other medical traditions. Iboga demonstrates potential in helping the cessation of opioid addiction by reducing opioid withdrawal (Wilson et al., 2020).

Knowledge gaps include more precise quantitative measures of the treatment effect, and the further development of best practices for iboga or ibogaine administration. Iboga and ibogaine assisted addictions treatment has evidence for treatment efficacy in small cohorts (Wilson et al., 2020). Additional insights are welcome into the mechanism of opioid addiction, and the mechanisms of iboga and ibogaine in diminishing opioid withdrawal symptoms (Antonio et al., 2013).

Further investigation is warranted, focused on determining the efficacy and safety of iboga and ibogaine for the treatment of OUD. Additionally, research can investigate how nontraditional treatment approaches can be adapted to individual patients.

Limitations of the Study

This study has the limitations of reporting research that may be subject to bias. While we provide an assessment of bias in the form of the Cochrane ROB2 analysis, this instrument may not capture possible fraud or data manipulation. Another limitation is that while this list provides a large list of potential compounds, and some prioritization, we leave mechanism out of this article for brevity. Studying the mechanisms of effective treatments could contribute to our greater understanding of treating opioid withdrawal, but we have left this out of the manuscript for brevity.

Additionally, our characterization of availability may not actually correspond to cost or availability. The analysis assumes that multi-component therapeutics of specialized herbal formulae are more difficult to acquire than single components, which is generally a safe assumption, but this changes significantly if one is located near a herbalist in the traditions of Chinese or Persian medicine, which are the traditions with interventions for opioid withdrawal symptoms.

Some treatment components may be difficult to translate from the traditional medical context of these traditions. We used machine translation of articles (DeepL.com), and it is possible that the unfamiliarity of the authors with these medical systems results in a lack of understanding of the treatments themselves. To avoid this possible lossy communication, we recommend readers find the referenced primary texts themselves.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHORS CONTRIBUTION

Matthew Halma: conceptualization, methodology, investigation, writing - original draft, writing, review and editing, supervision.
Cristoph Hesse: formal analysis.
Edgar Selem: investigation.
Joseph Varon: conceptualization and writing - review and editing.

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SUPPLEMENTARY INFORMATION

The authors of this article provided supplementary materialresulting from the literature review

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