

REVIEW

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Substance use disorders (SUDs) in Latin America and the Caribbean: a narrative review of native medicinal plants as alternative therapies

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Abstract

Background Latin America and the Caribbean region are currently faced with the challenges of drug and substance use leading to violence and crime, especially among the younger populations. The complex nature of substance use disorder (SUD), the cost and adverse effects of conventional therapies, the deeply rooted cultural practices of medicinal plants usage, and the abundance of rainforest flora and fauna in Latin America and the Caribbean (LAC) are incentives for exploring bioactive compounds in managing SUDs. This review presented native medicinal plants traditionally used for managing SUD in LAC.

Main body.

Articles indexed with Google Scholar, EBSCOhost, Scopus, SciELO, Web of Science, PubMed, PubMed Central, and LILACS databases and gray literature like PAHO, WHO, and CICAD were searched for medicinal plants used in drug addiction. Medicinal plants native to LAC or naturalized and cultivated in the region were included in the study. Twelve medicinal plants belonging to 10 families were identified with potential mechanisms for SUD management and described in this review. The families and plants include Acoraceae (*Acorus calamus* L.), Malpighiaceae (*Banisteriopsis caapi* [Spruce ex Griseb.]), Hypericaceae (*Hypericum perforatum* L.), Asteraceae (*Mikania glomerata* Spreng; *Matricaria recutita* L.), Passifloraceae (*Passiflora caerulea* L.), Piperaceae (*Piper methysticum* L.f.), Crassulaceae (*Rhodiola rosea* L.), Lamiaceae (*Scutellaria lateriflora* L.; *Leonotis nepetifolia* (L.) R.Br.), Turneraceae (*Turnera diffusa* Willd. ex Schult.), and Zingiberaceae (*Zingiber officinale* var. *officinale*). Most plants produce their ethnopharmacological effects through GABergic activity, opioid receptor interaction, neurotransmitter modulation, NMDA receptor antagonism, antioxidant/anti-inflammatory activity, or through the enhancement of neuroplasticity—pathways for mitigating substance use disorders.

Conclusion The abundance of rich rainforest medicinal plants in LAC makes them cost-effective alternatives in managing SUD, especially since they are easily accessible and have traditionally proven effective with fewer adverse effects. Reviewed preclinical and clinical studies reveal that select medicinal plants such as *B. caapi* and *H. perforatum* may modulate addiction-related neurochemical pathways, curb cravings, and mitigate withdrawal symptoms among substance addiction populations. However, clinical validation of the medicinal plants remains limited, revealing a disconnect between traditional ethnomedical use and current scientific evidence.

Keywords Medicinal plants, Substance use disorders, Drug addiction, Drug dependence, Caribbean, Latin America

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1 Background

Substance use disorder (SUD) is a chronic, relapsing medical condition characterized by the compulsive use of one or more substances such as alcohol, illicit drugs (e.g., cocaine, opioids), prescription medicines (e.g., benzodiazepines, stimulants), and other substances (e.g., cannabis), despite significant harm or adverse consequences. Diagnoses are mainly based on a cluster of physiological, cognitive, and behavioral symptoms, as outlined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Utilizing psychotropic substances, narcotics, or psychoactive drugs without recreation or medical supervision poses significant health risks to public health [1]. For instance, cannabis, heroin, and cocaine were traditionally plant-based psychoactive drugs grown and consumed within specified regions, but increased globalization has caused a prevalent use of these substances, and today, illegal laboratories are synthesizing new and more dangerous psychoactive drugs consumed widely [1]. In 2017, approximately 5.5% (about 271 million people) aged 15–64 had consumed illicit drugs at least once, while globally, about 0.7% of the adult population (about 35 million people) of substance users suffer from drug use disorders (SUD) [1]. Although psychotropics have gone through a rigorous drug development process, offer safety due to their monitored use, and are regulated in most jurisdictions, most psychostimulants, hypnotics, anxiolytics, and synthetic opioid analgesics cause a proportion of substance abuse disorders due to the non-medical use of prescription drugs. In 2017, substance use was attributed to about half a million deaths globally [2]. In the Americas, the United Nations Office on Drugs and Crime (UNODC) reported that amphetamines, cannabis, cocaine, opioids, and other stimulants are the main drugs used by approximately 83 million persons, with an estimated 87 million predicted to use them by the year 2030 [3].

In Latin America and the Caribbean (LAC), at some point in their lifetime, approximately 1.2 million women and 4.4 men are affected by SUD, including related health conditions and drug dependence [4, 5]. Therefore, drug use among the youths and the general population is a significant challenge to policymakers in Latin America and the Caribbean [6].

Latin America and the Caribbean are culturally, economically, linguistically, and ethnically diverse. In addition, LAC is highly diverse in flora and fauna due to the region's rich rainforest, especially the Amazon. The Inter-American Drug Abuse Control Commission reported that opioids, cocaine, inhalants, cannabis, tobacco and electronic cigarettes, alcohol, and prescription drugs are the most reported abused substances in Latin America and the Caribbean [7]. For instance, the increase in the

demand for the treatment of SUD due to cannabis use and other related cannabis health challenges has been reported [2]. Within the LAC region, cannabis is used by approximately 5% of the population in 15 countries, with Jamaica and Chile reported to have the highest (15%) prevalence of cannabis use when compared to Uruguay (9%) and Argentina (8%). In contrast, countries like Bolivia, Ecuador, and Panama had a one percent prevalence consumption rate [2].

Conversely, substance use and substance use disorders are a significant concern because they are directly linked to mental health disorders and other health challenges that are currently adding to the burden of the strained healthcare systems in the region. Mental and neurological disorders such as dementia, suicide, and substance use disorders have been reported to affect around 200 million in the Western Pacific Region [8]. As part of its effort to address these challenges, The Pan American Health Organization (PAHO) and the World Health Organization (WHO) launched a project recently to improve policies on substance use disorders in LAC [9]. The capacity-building project aims to design and employ social and health responses for substance use-related challenges in the region, specifically in Panama, Jamaica, Guyana, Ecuador, Costa Rica, and Colombia.

The management of SUD is often complex, but the objective is to help people recover by improving their quality of life and general health. Therapy goals should include reducing relapse and the risk of complications leading to future harm, improving social function, well-being, and health, and the ultimate reduction or eventual stoppage of substance use [1]. To date, suggested SUD therapies include pharmacotherapy, the 12-step program, multicomponent psychosocial treatment, cognitive behavioral therapy, family-based therapy, yoga, and other culturally based programs [10, 11]. Relatedly, therapeutic communities combine the above and other spiritual, cultic, or medicinal plants in managing SUD, some with successful testimonies [12, 13]. Therapeutic communities are drug-free, structured, and organized live-in residential environments that foster and encourage change toward recovery from SUD and ultimate community reintegration of the patient [14]. The use of medicinal plants in some therapeutic communities has been reported [15]. For instance, medicinal plants are part of the Wat Thamkrabok Buddhist monastery drug rehabilitation program in Thailand, where sacred vows, strict disciples, herbal saunas, and induction of vomiting to relieve drug craving are employed as unconventional methods to treat SUDS [16]. The Wat Thamkrabok substance abuse rehabilitation program claims a 70% success rate since its inception in 1959.

Similarly, in Gabon, West Africa, the medicinal plant *Tabernanthe iboga* Baill is used as part of the spiritual treatment of SUD [17]. Ibogaine (the plant's bioactive compound) therapy is a natural and holistic remedy that utilizes a psychoactive chemical to treat diverse drug addictions. Ibogaine can eliminate withdrawal symptoms and cravings by blocking the opioid receptors in the brain [17]. In addition, the plant extract is also reported to induce a psychedelic state lasting up to 36 h, during which patients may experience psychological clarity and introspection to help them deal with their fears, traumas, and causes of their addictions [18, 19].

In Latin America, on the other hand, the Takiwasi Center for Addiction Treatment and Rehabilitation in Peru utilizes traditional Amazonian medicine to treat SUDs [20, 21]. The therapy involves ritual techniques indigenous to the Amazon rainforest, where SUD treatment protocol combines Amazonian traditional medicine with Western psychotherapy, conducting healing ceremonies, dietary retreats, and purging rituals with emetic plants [20]. The primary Amazonian rainforest plants used in the Takiwasi treatment protocol are purgahuasca and ayahuasca from the *Banisteriopsis caapi* (Spruce ex Griseb.) vine. *B. caapi* has been reported as a potential medicinal plant for managing SUD, especially among tribes of the Northwestern Amazonian regions of Peru, Ecuador, Colombia, and Brazil [17].

Latin America and the Caribbean are rich in vegetation biodiversity and famous for medicinal plants renowned for the prevention and management of diverse diseases [22–27]. Also, medicinal plants have provided valuable insights into scientific knowledge, and their bioactive compounds have resulted in the discovery of many modern medicines that greatly benefit public health [28, 29]. While advancement in chemistry and computers is helping to unravel the numerous complex alkaloids found in medicinal plants, indigenous people will continue to use them to prevent and treat many disease conditions, including SUD. Furthermore, with increased awareness of medicinal plants' benefits, perceived safety, availability, ease of access, cultural beliefs, and reasonably priced, persons in LAC will continue to explore medicinal plants to prevent and treat various disease conditions. Because medicinal plants still provide significant pharmacological targets for the discovery of new molecules, this review attempts to present the biodiverse therapeutic plant resources available as potential alternatives for the management of SUD in LAC, especially that SUD treatments with Western conventional medicines alone has posed challenges to healthcare personal, patients, and the public in LAC.

2 Methodology

2.1 Data search approach

In tandem with the review's focus to synthesize diverse perspectives on potential medicinal plants as alternatives for SUD management in LAC, we included databases like LILACS and SciELO to ensure representation on region-specific policy challenges, cultural factors, and epidemiological trends in SUD. Databases with multidisciplinary coverage like PubMed, Scopus, Google Scholar, etc., were included in the review to access global evidence on SUD mechanisms and validated interventions with LAC contexts. Finally, gray literature such as CICAD and PAHO contain theses from universities and government reports from the region that address gaps of peer-reviewed data on traditional or informal SUD management, especially within LAC environments. Technical, subscription-only, or databases focused on health topics only were excluded due to irrelevance to SUD management. Studies (2000–2024) reporting preclinical and clinical data on SUD mechanisms, with a regional focus on LAC, were included. This approach balances feasibility depth, aligning with the review's goal of contextualizing SUD management within LAC geographical, sociocultural, and healthcare landscapes.

2.2 Database search

Ultimately, articles indexed with Google Scholar, EBSCOhost, Scopus, SciELO, Web of Science, PubMed, PubMed Central, and LILACS databases and gray literature like PAHO, WHO, and CICAD were searched using the primary search term "plants used to treat/manage substance disorders in Latin America and the Caribbean" and secondary search terms "substance use disorders" "plant-based therapies for SUD," "Drug dependence," "Drug addiction," "Substance use," "alcohol dependence," "Opioids addiction," "Cocaine addiction," "marijuana addiction," "Traditional medicinal plants for the treatment of drug addiction," "therapeutic communities in LAC," "medicinal plants used by therapeutic communities in LAC," and "complementary and alternative therapies for substance use disorders for inclusion in the current review." Search strings included ("medicinal plants" OR "herbal medicine") AND ("substance use disorder" OR "addiction") AND ("Latin America" OR "Caribbean"). Out of the 1,155 articles searched, 45 articles were eventually included studies.

3 Main body

3.1 Results

In total, the database search yielded 1,155 articles, but after applying the inclusion criteria, only 45 articles were found relevant and included in the narrative review. Many of the excluded studies were reviews without

original data, or studies on general ethnobotanical surveys not relevant to SUD. Included studies have geographical focus, English language, and specifically SUD relevance, addressing ethnobotanical surveys indicating traditional use for addiction or preclinical/clinical evidence on relevant mechanisms such as GABA modulation. Gray literature like CICAD or PAHO had relevant policy documents. The 45 included studies reflect mechanistic relevance and regional specificity, while the excluded articles lacked robust methodology or direct applicability.

Ultimately, 12 medicinal plants belonging to 10 families were identified with potential mechanisms for SUD management and described in this review (Table 1). The families and plants include Acoraceae (*Acorus calamus* L.), Malpighiaceae (*Banisteriopsis caapi* [Spruce ex Griseb.]), Hypericaceae (*Hypericum perforatum* L.), Asteraceae (*Mikania glomerata* Spreng; *Matricaria recutita* L.), Passifloraceae (*Passiflora caerulea* L.), Piperaceae (*Piper methysticum* L.f.), Crassulaceae (*Rhodiola rosea* L.), Lamiaceae (*Scutellaria lateriflora* L.; *Leonotis nepetifolia* (L.) R.Br.), Turneraceae (*Turnera diffusa* Willd. ex Schult.), and Zingiberaceae (*Zingiber officinale* var. *officinale*). A synthesis of the plants traditional applications, bioactive compounds, pharmacology, mechanism of action, and safety based on peer-reviewed evidence is described below and summarized in Tables 1, 2, 3 and 4.

3.1.1 *Acorus calamus* L (Calamo) [Acoraceae]

The *Acorus calamus*, also known locally as calamo, is a wetland monocot of the Acoraceae family in the genus *Acorus*. *A. calamus* is traditionally used to treat a wide range of illnesses such as liver, kidney, metabolic, respiratory, gastrointestinal, neurological disorders diuretic, carminative, laxative, and as a sedative [30]. Although the plant is distributed in several parts of the world, traditionally it was practiced in the Chinese system of medicine and the Indian Ayurvedic tradition for neurological, respiratory, and gastrointestinal disorders (Table 2). Additionally, the plant is used as analgesic, tonic, antipyretic, skin diseases, and other health challenges. Evidence of its neurological and metabolic effects antiobesity, neuroprotective, immunomodulatory, anti-inflammatory, anticonvulsants, antihypertensive, and antidepressants exists [31].

Calamus oil is an essential oil obtained from different parts of the plant, and it contains the phenolic ether called Asarone (Table 1). Asarone is found to be a major (up to 96%) and active constituent of the essential oil [32, 33]. The essential oil in *A. calamus* (Asarone) is considered the central active ingredient used as spice and for medicine. Other components include alkaloids, flavonoids, phenylpropanoids, and terpenoids (Table 3)

[34] *A. calamus* has been reported to possess both anti-convulsant and neuroprotective properties in animal studies and has been traditionally used for those purposes [35]. Pages et al. [36] demonstrated that *A. calamus* significantly potentiated pentobarbital-induced sleep caused hypothermia, and reduced locomotor activity, while lessening treadmill performance when 100 mg/kg was administered using pentylenetetrazol-induced convulsion technique. Doses are derived from animal studies; human equivalency requires further pharmacokinetic studies. Furthermore, the latency-induced pentylenetetrazol latency period seizures significantly increased using *A. calamus* methanol extract [36]. Also, Gama amino butyric acid (GABA) was potentiated by *A. calamus* root extract, supporting the plant's anticonvulsant effects (Table 3) [37]. Additionally, *A. calamus*'s tranquilizing and sedative activity, as well as its ability to spontaneously antagonize motor activity, has been reported in animal studies with doses of 10–50 mg/kg, supporting the claim for its ability to counteract the effect of mental stress [38]. In a recent review, Sharma et al. [31] summarized that the antidepressant activity of *A. calamus* could be linked to its interaction with serotonergic, dopaminergic, adrenergic, and GABAergic systems in the brain (Table 4). Also, the immobility period of the forced swim test (FST) and tail suspension test (TST) were reported to be significantly decreased using *A. calamus* extract [39].

Specifically, as an antidepressant, *A. calamus* increases α_1 and α_2 adrenergic and 5-HT_{1A} serotonergic modulation. As an anxiolytic, the biotic compound α -Asarone increases the down-regulation of GABA_A receptors decreasing the up-regulation of GluR1-containing AMPA and NMDA receptors [123]. Furthermore, decrease in GABA-T and increase the levels of GABA, GAD67, and GABAAR-mRNA expression have been reported in the temporal lobe in epilepsy (Table 4). However, in the mitral cells, decrease in Na⁺ channel blockade with an increase in the down-regulation of GABA_A receptors have been reported in epilepsy [123]. Also, High affinity binding to the central benzodiazepine receptors gives *A. calamus* its significant antidepressive and anxiolytic effects [127]. The antiepileptic, antidepressant, and antianxiety effects of *A. calamus* could be explored as alternative therapies in the management of SUD patients, especially in LAC [40]. Although *A. calamus* has low toxicity in low concentrations, β -asarone compound has shown carcinogenic and toxic activities [128]. Overall, no noticeable data on *A. calamus* toxicity have been reported in traditional use based on several investigations [31].

Table 1 Medicinal plants with potentials for SUD management in LAC

Plant name	Family	Active compounds	Traditional uses	Study status (SUD)	Mechanism and SUD applications	References
<i>Acorus calamus</i> (Calamo)	Acoraceae	Asarone, flavonoids, alkaloids	Sedative, anticonvulsant, digestive aid; used for neurological disorders in Ayurveda	Preclinical (animal studies)	GABAergic activity; reduces anxiety, seizures, and withdrawal	[30–40]
<i>Banisteriopsis caapi</i> (Ayahuasca)	Malpighiaceae	β-Carbolines (harmine, tetrahydroharmine), DMT	Spiritual rituals, purging ceremonies; Amazonian tribes for addiction and mental clarity	Preclinical (ethnopharmacological); Limited clinical (observational reports)	MAO-A inhibition; psychedelic therapy for addiction	[20, 21, 41–44]
<i>Hypericum perforatum</i> (St. John's Wort)	Hypericaceae	Hypericin, hyperforin, flavonoids	Depression, anxiety, wound healing; European and LAC folk medicine	Preclinical (SUD animal models); Clinical (depression)	Reduces opioid withdrawal symptoms; inhibits neurotransmitter reuptake	[45–50]
<i>Mikania glomerata</i> (Guaco)	Asteraceae	Diterpenes, ent-kaurene	Respiratory ailments (asthma, bronchitis), anti-inflammatory; Brazilian traditional medicine	Preclinical (anxiety models)	GABAergic modulation; anxiolytic effects	[51–57]
<i>Matricaria recutita</i> (Chamomile)	Asteraceae	Flavonoids, apigenin	Anxiety, insomnia, gastrointestinal issues; used in European and LAC herbalism	Clinical (anxiety/sleep trials)	GABA modulation; improves sleep quality in withdrawal	[58–71]
<i>Passiflora caerulea</i> (Flor de Passion)	Passifloraceae	β-Carbolines, flavonoids (chrysin)	Sedative, anxiolytic; Andean cultures for calming nerves and sleep aid	Preclinical (rodent studies)	GABA _A modulation; reduces benzodiazepine dependence	[58, 72–80]
<i>Piper methysticum</i> (Kava)	Piperaceae	Kavalactones (yangonin, methysticin)	Ceremonial drink (Pacific Islands); stress relief, muscle relaxation in LAC	Clinical (anxiety/stress trials)	Enhances GABA _A activity; reduces stress during withdrawal	[78, 81–86]
<i>Rhodiola rosea</i> (Golden Root)	Crassulaceae	Salidroside, rosavin	Adaptogen for fatigue, altitude sickness; Siberian and Andean traditional medicine	Preclinical (stress models)	Adaptogenic; reduces cortisol and oxidative stress in withdrawal	[87–91]
<i>Scutellaria lateriflora</i> (Skullcap)	Lamiaceae	Baicalin, wogonin	Nervous system disorders (insomnia, epilepsy); Native American and LAC herbalism	Preclinical (animal models)	GABA _A binding; neuroprotection against withdrawal seizures	[92–94]
<i>Leonotis nepetifolia</i> (Dagga)	Lamiaceae	Terpenoids, verbascoside	Pain relief, anxiety, respiratory issues; African and Caribbean traditional medicine	Preclinical (animal studies)	Antioxidant; reduces anxiety and neuroinflammation	[95–101]
<i>Turnera diffusa</i> (Damiana)	Turneraceae (Turneraceae is recognized here based on traditional classification, though recent taxonomic revisions place Turnera within Passifloraceae)	Flavonoids (apigenin), arbutin	Aphrodisiac, mood enhancer; Mayan and Mexican traditional medicine	Preclinical (rodent anxiety models)	GABA _A modulation; MAO inhibition for mood stabilization	[102–110]
<i>Zingiber officinale</i> (Ginger)	Zingiberaceae	Gingerols, shogaols	Digestive aid, anti-inflammatory; used in Ayurveda, Caribbean, and South American folk medicine	Preclinical (oxidative stress models)	Reduces alcohol-induced neuroinflammation and oxidative damage	[111–122]

Table 2 Synthesis of medicinal plants by region in Latin America and the Caribbean (LAC) for SUD management

Region	Medicinal Plant	Traditional Usage for SUD Management	References
Amazonian/South America	<i>Banisteriopsis caapi</i> (Ayahuasca)	Used in Amazonian traditional medicine (Peru, Ecuador, Colombia, Brazil) for addiction treatment via Ayahuasca ceremonies. Modulates monoamine oxidase (MAO) and serotonergic pathways to reduce cravings and withdrawal	[20, 21, 41–44]
Amazonian/South America	<i>Mikania glomerata</i> (Guaco)	Native to Brazil; anxiolytic and GABAergic effects reduce anxiety and withdrawal symptoms. Used in respiratory and neurological disorders	[51–57]
Amazonian/South America	<i>Passiflora caerulea</i> (Flor de Passion)	Distributed in South and Central America. Sedative and anxiolytic effects via GABA modulation. Used for opioid dependence and withdrawal	[58, 72–77]
Caribbean	<i>Leonotis nepetifolia</i> (Dagga, Lion's Ear)	Used in Trinidad for stress and anxiety disorders. GABAergic modulation and neuroprotective effects mitigate withdrawal symptoms	[95–101]
Caribbean	<i>Turnera diffusa</i> (Damiana)	Traditional aphrodisiac and anxiolytic in Caribbean communities. Modulates serotonin and GABA pathways to reduce cravings	[102–110]
Central America and other LAC regions	<i>Zingiber officinale</i> (Ginger)	Cultivated broadly in LAC but lacks region-specific clinical data. Demonstrates antioxidant and anti-inflammatory properties protect against neurotoxicity from substance use. Used in alcohol and opioid withdrawal	[111–122]
Andean	<i>Rhodiola rosea</i> (Golden Root)	Naturalized in high-altitude regions. Adaptogenic effects stabilize mood, reduce stress, and normalize cortisol levels during withdrawal	[87–91]
Various LAC Regions	<i>Acorus calamus</i> (Calamo)	Used for neurological disorders; GABAergic and serotonergic activity reduces anxiety and seizures linked to SUD	[30–40]
Various LAC Regions	<i>Hypericum perforatum</i> (St. John's Wort)	Naturalized in temperate zones. Inhibits neurotransmitter reuptake (serotonin, dopamine) to alleviate opioid and nicotine withdrawal	[45–50]
Various LAC Regions	<i>Matricaria recutita</i> (Chamomile)	Widely used for anxiety and sleep disorders. GABAergic and antioxidant effects mitigate withdrawal-related stress	[58–71]
Pacific/Central America	<i>Piper methysticum</i> (Kava)	Naturalized in the Americas. Enhances GABA activity and reduces anxiety during withdrawal without dependency	[78, 81–86]
Northern LAC	<i>Scutellaria lateriflora</i> (Skullcap)	Used in Mexico and Central America for neurological disorders. GABA modulation reduces seizures and anxiety in SUD	[92–94]

Traditionally, most of the identified plants in Table 1 are rooted in treating anxiety, insomnia, or digestive issues, which indirectly align with SUD withdrawal symptoms (e.g., anxiety, stress). Only *Banisteriopsis caapi* (ayahuasca) and *Hypericum perforatum* have limited clinical reports; others rely on preclinical or non-SUD clinical data highlighting the need for targeted research. Mechanistic overlap was noted where plants like *Passiflora* and *Kava* target GABA pathways, mimicking benzodiazepines but with lower dependence risk. Most plants have preclinical evidence from animal or in vitro studies but lack human trials for SUD. Clinical studies were limited to non-SUD applications (e.g., anxiety, depression) unless specified.

Table 2 synthesizes the geographical distribution, traditional applications, and pharmacological pathways of medicinal plants in LAC for SUD management. Some plants (e.g., *Zingiber officinale*) are broadly cultivated across LAC but lack specific regional attribution in the review. These are categorized under "Various LAC Regions." Traditional use focuses on mechanisms relevant to SUD (e.g., GABA modulation, antioxidant activity).

Table 3 presents individual psychoactive compounds with their potential for SUD management. Mechanistically, compounds are linked to SUD management via pathways like GABA modulation, MAO inhibition, serotonin/dopamine stabilization, and neuroprotection.

Table 3 Identified medicinal plants psychoactive compounds and their potential role in SUD

Psychoactive Compound	Type	Plant Name	Potential for SUD Management	References
Asarone (α/β -Asarone)	Phenolic Ether	<i>Acorus calamus</i> (Calamo)	GABAergic activity reduces anxiety/seizures; modulates serotonin/dopamine pathways to stabilize mood	[30–40]
β -Carbolines	Alkaloids	<i>Banisteriopsis caapi</i> (Ayahuasca)	Inhibits MAO-A, allowing DMT to activate serotonin receptors; reduces cravings and withdrawal	[20, 21, 41–44]
- Harmine	Alkaloid	<i>Banisteriopsis caapi</i>	MAO-A inhibition prolongs serotonin/DMT effects; antiaddictive properties	[41–44]
- Harmaline	Alkaloid	<i>Banisteriopsis caapi</i>	Enhances DMT bioavailability; mitigates withdrawal via serotonin modulation	[41–44]
- Tetrahydroharmine (THH)	Alkaloid	<i>Banisteriopsis caapi</i>	Reduces anxiety and potentiates DMT's therapeutic effects	[41–44]
- Harmalol	Alkaloid	<i>Banisteriopsis caapi</i>	Antioxidant/anti-inflammatory effects protect against neurotoxicity from substance use	[41–44]
DMT (<i>N,N</i> -Dimethyltryptamine)	Tryptamine Alkaloid	<i>Banisteriopsis caapi</i> (Ayahuasca)	Activates 5-HT _{2A} receptors for introspective healing; reduces relapse risk	[41–44]
Hypericin/Hyperforin	Naphthodianthrone	<i>Hypericum perforatum</i> (St. John's Wort)	Inhibits serotonin/norepinephrine reuptake; alleviates opioid/nicotine withdrawal symptoms	[45–50]
Rutin	Flavonoid	<i>Hypericum perforatum</i>	Antioxidant properties reduce oxidative stress linked to addiction	[45–50]
Ent-kaurene	Diterpene	<i>Mikania glomerata</i> (Guaco)	Anxiolytic via GABA _A receptor interaction; reduces stress-induced cravings	[51–57]
Flavonoids (e.g., Apigenin)	Flavonoids	<i>Matricaria recutita</i> (Chamomile)	GABA _A receptor modulation and antioxidant effects reduce anxiety and withdrawal-related stress	[58–71]
β -Carbolines (Harmene)	Alkaloids	<i>Passiflora caerulea</i> (Passionflower)	Binds to benzodiazepine sites on GABA _A receptors; reduces anxiety and hyperexcitability	[58, 72–80]
Quercetin	Flavonoid	<i>Passiflora caerulea</i>	Antioxidant/anti-inflammatory effects protect neurons from substance-induced damage	[72–80]
Chrysin	Flavonoid	<i>Passiflora caerulea</i>	Mimics benzodiazepines by enhancing GABAergic transmission; reduces withdrawal seizures	[72–80]
Kavalactones	Lactones	<i>Piper methysticum</i> (Kava)	Enhances GABA _A activity without dependency; reduces anxiety and opioid reliance	[78, 81–85]
Salidroside	Phenylethanoid Glycoside	<i>Rhodiola rosea</i> (Golden Root)	Adaptogenic effects stabilize HPA axis; reduces cortisol and cravings during withdrawal	[87–91]
Baicalin/Wogonin	Flavonoids	<i>Scutellaria lateriflora</i> (Skullcap)	Binds to GABA _A benzodiazepine sites; anticonvulsant and anxiolytic for alcohol/opioid withdrawal	[92–94]
Leonurine	Alkaloid	<i>Leonotis nepetifolia</i> (Lion's Ear)	GABA _A modulation and antioxidant activity mitigate stress-induced relapse	[95–101]
Arbutin	Glycoside	<i>Turnera diffusa</i> (Damiana)	Serotonergic modulation reduces anxiety and dysphoria linked to withdrawal	[102–110]
Gingerols/Shogaols	Phenolic Compounds	<i>Zingiber officinale</i> (Ginger)	Antioxidant/anti-inflammatory effects protect against neurotoxicity; reduces oxidative stress	[111–122]

Table 4 Summary of plants mechanism of action and their role in SUD management

Mechanism	Examples of Plants	Role in SUD Management	Reference
GABAergic Activity	<i>Acorus calamus</i> , <i>Passiflora caerulea</i> , Kava	Animal models indicate that the plants reduce anxiety, seizures, and withdrawal symptoms	[46, 47, 49, 73, 80]
Opioid Receptor Interaction	<i>Hypericum perforatum</i> , <i>Leonotis nepetifolia</i>	Preclinical evidence suggests that the plants alleviates opioid withdrawal and cravings	[31, 36, 37, 98–101]
Neurotransmitter Modulation	<i>Hypericum perforatum</i> , <i>Acorus calamus</i>	Preclinical evidence suggests that the plants stabilizes mood and reduces depressive symptoms	[31, 39, 123, 46, 47, 49]
NMDA Receptor Antagonism	<i>Mikania glomerata</i> , <i>Rhodiola rosea</i>	Animal models indicate the plants mitigate excitotoxicity and withdrawal effects	[52, 55, 91, 124]
Antioxidant/anti-inflammatory	Ginger, Chamomile, <i>Rhodiola rosea</i>	Protects neurons from oxidative damage	[70, 71, 115–117, 124]
Neuroplasticity enhancement	<i>Rhodiola rosea</i> , <i>Banisteriopsis caapi</i>	Preclinical evidence suggests that the plants supports neural repair and stress resilience	[43, 91, 124–126]

Highlighted actions for withdrawal symptoms include reducing anxiety, seizures, cravings, and oxidative stress during withdrawal. Some plants (e.g., *Banisteriopsis caapi*, *Hypericum perforatum*) have preclinical/clinical evidence, while others rely on traditional use and mechanistic plausibility.

Table 4 summarizes the mechanism of action of some of the plants with potential for SUD management. GABAergic Activity: Reduces anxiety and seizures (e.g., *Acorus calamus*, *Passiflora caerulea*). Neurotransmitter Modulation: Stabilizes mood (e.g., *Hypericum perforatum*, *Rhodiola rosea*). MAO Inhibition: Prevents relapse by elevating monoamines (e.g., *Banisteriopsis caapi*, *Turnera diffusa*). Antioxidant/anti-inflammatory: Protects neurons from oxidative damage (e.g., *Zingiber officinale*, *Matricaria recutita*).

3.1.2 *Banisteriopsis caapi* [Spruce ex Griseb.] (Ayahuasca) [Malpighiaceae]

Banisteriopsis caapi is a medicinal plant found in LAC that is uniquely reported to be used in managing substance use disorders (SUD). *B. caapi*, is one of the main active ingredient in ayahuasca, a natural psychoactive preparation used for therapeutic, religious, and ethnic rituals in LAC countries such as Ecuador, Colombia, Peru, and Brazil. *Psychotria viridis* Ruiz and Pav and *Banisteriopsis caapi* are the main ingredients in ayahuasca prepared through a prolonged decoction process of the leaves (Table 2) [21]. The ayahuasca brew containing the leaves and stems of *B. caapi* with other plants (*Psychotria viridis* Ruiz and Pav) has β -carbolines as a significant compound with psychoactive activity within the remedy [41]. The bark and stem of *B. caapi* containing β -carbolines alkaloids and the leaves of *P. viridis* rich in *N, N*-dimethyltryptamine (DMT) are the significant sources of the psychoactive compounds available in the aqueous extract of ayahuasca. Harmaline, tetrahydroharmine, and harmine (hamala alkaloids) are the potent

alkaloids found in *B. caapi* linked to antidepressant activity (Table 3) [125]. Also, β -carbolines such as harmaline, tetrahydroharmine (THH), and harmine contain an abundance of tryptamine hallucinogen *N, N*-dimethyltryptamine (DMT) [125]. The ability for β -carbolines to increase monoamine levels by reversibly inhibiting peripheral monoamine oxidase type A (MAO-A) is the major mechanism of action of *B. caapi*. This inhibition of MAO-A allows *N, N*-dimethyltryptamine to reach the brain (DMT is not active orally) where it act on layer V neurons of cortical areas related to emotional processing and introspection to antagonize serotonergic 5-HT_{2A} receptors (Table 3). Monoamine oxidase inhibitors are used in the management of different mental disorders such as depression, social phobia, panic, anxiety, and other nervous system disorders [126].

In a recent publication, Brito-da-Costa et al. [43] summarized the mechanism of action of *B. caapi* in psychiatric and mental disorders to be attributed to the ability of the hamala alkaloids to potently inhibit monoamine oxidase A potently, thereby inhibiting the extensive metabolism of *N, N*-dimethyltryptamine to 3-indole-acetic acid. This synergic process allows adequate *N, N*-dimethyltryptamine to interact and stimulate non-serotonergic and serotonergic receptors in the brain related to psychotropic activity [43]. Furthermore, studies have shown evidence that ayahuasca has excellent potential for the management of substance use disorders, anxiety, and depression more so that the alkaloids do not lead to tolerance or dependence, making the alkaloids beneficial for psychotherapy (Table 3) [43]. The use of medicinal plants in Takiwasi's treatment protocol in Peru, South America, incorporates the purgahuasca and ayahuasca along with traditional Amazonian therapies to treat SUD [20, 21].

In a recent thematic review, White et al. [44] surmised that though some adverse human events have been reported with ayahuasca generally, data showed that DMT is safe in traditional usage. Teratogenic and

abortifacient effects have been shown with higher doses of ayahuasca using animal models. Also, evidence of toxicities with higher doses of isolated harmala alkaloids which may increase in polypharmacy with certain drugs have been reported. Overall, preclinical models in ayahuasca studies showed harmaline to have the most issues (White et al., 2024) [44]. The acceptable traditional uses and positive scientific reports of these medicinal plants, especially, in Latin America make them potential candidates as alternative therapies for SUD management.

3.1.3 *Hypericum perforatum* L. (St. John's Wort) [Hypericaceae]

Hypericum perforatum was originally native to North Africa, Western Asia, and Europe. However, presently the plant is naturalized and cultivated in most temperate regions of the world, including Latin America and the Caribbean (Table 2). Traditionally, the leaves and flowers of *Hypericum perforatum* have been used as medicinal plants in the management of anxiety and depression (Table 1). The plant extract contains many polyphenols, including phloroglucinols (adhyperforin, hyperforin), phenolic acids, naphthodianthrones (e.g., pseudohypericin, hypericin, protohypericin), and flavonoids (e.g., quercetin, hyperoside, quercitrin, isoquercetin, rutin) (Table 3) [45]. Presently, hyperforin, pseudohypericin, and hypericin are the most bioactive candidates of interest for the herb's antidepressant activity (Table 4). This shows evidence in the management of patients with mild-to-moderate depression in controlled clinical trials. The antidepressant activity of *H. perforatum* is significantly associated with hyperforin, which can inhibit L-glutamate, GABA, and synaptosomal uptake of the amino acid transmitters [46]. Although traditionally, the plant has been used for managing affective disorders, its benefit in managing substance addiction has been reported (Table 1). In 2007, Mannucci et al. [47] reported the beneficial effect of *H. perforatum* to significantly reducing nicotine withdrawal dependence in mice by increasing cortical serotonin levels and a significant increase in serotonin 5-HT_{1A} receptors. Similarly, naloxone-induced heroin withdrawal effects were reported with *H. perforatum*, where the extracts showed a substantial reduction in vocalization on touch during withdrawal in rats, evidenced by the plant's capability to reduce the physical signs associated with opiate withdrawal [48]. Relatedly, Feily and Abbasi [49] suggested that *H. perforatum* may have human therapeutic benefits in opiate withdrawal syndrome after the plant extract significantly attenuated morphine withdrawal signs. Most recently, Fugazzotto et al. [50] recommended using *H. perforatum* as a natural therapy for cocaine addiction when the plant showed

a significant reduction in the rewarding effects in mice while preventing the stress-induced reinstatement of cocaine-induced conditioned place preference.

Photosensitivity, dizziness, GI upset, fatigue, confusion, and anxiety are some of the reported adverse effects of the herbal remedy. Current data did not convincingly implicate *H. perforatum* as an apparent clinically significant hepatotoxicant but has effects on P-glycoprotein, the major drug transport protein and the cytochrome P450 systems where it induces 2C0 and CYP3A4 [129, 130]. In addition, it has major drug interactions particularly with psychotropic agents, anticoagulants, platelet inhibitors, contraceptives, digoxin, and antiretroviral drugs [129, 131]. In the USA, St. John's Wort is currently available as an over-the-counter (OTC) herbal supplement [132]. Summarily, the ability of St. John's Wort to inhibit the reuptake of neurotransmitters such as norepinephrine, dopamine, and serotonin thereby increasing the concentration of the neurotransmitters at the synapses is beneficial in depression and SUD management (Table 4). In addition, St. John's Wort lowers depression by binding to GABA receptors to decrease the binding of GABA, a key pathway for exploring potential for SUD management [132]. The traditional outcomes of *H. perforatum* and the current reported animal studies indicate that the plant could be a strong alternative to substance use disorders in Latin America and the Caribbean.

3.1.4 *Mikania glomerata* Spreng (guaco) [Asteraceae]

In Brazil, South America, the native Indians have used the medicinal plant *Mikania glomerata* and *Mikania laevigata* (guaco) and many other genera of the *Mikania* of the Asteraceae family for the management of a wide variety of ailments [51, 52]. Approximately 450 species of the plant are found spread in the South American countries (Bolivia, the Andes, and Colombia), African and Asian countries, and is beneficial as antiallergic, anti-malarial, antiasthmatic, antipyretic, antirheumatic, and anti-inflammatory (Table 1) [51, 54]. Similar composition of the plant's bioactive compounds has been reported to include essential oils, diterpenes, lactones, coumarins, cinnamic acids, steroids, triterpenes, sesquiterpenes, and diterpene acids, majorly ent-kaurene (Table 3) [51, 53, 54]. Although traditionally used mainly in the management of respiratory disorders (cough, asthma, bronchitis) due to its immunomodulatory effects and its ability to decrease neutrophil migration and edema linked to the nitric oxide pathway, of recently, the plant has been implicated for their anxiolytic tendencies with the potentials for use in SUD [55]. Besides its antioxidant properties, *M. glomerata* demonstrated antianxiety activity (similar to diazepam) in mice at 200, 300, and 400 mg/kg doses by increasing the residence time in

the light compartment [55]. The study further reported that the anxiolytic ethanol extract effect of the leaves of *P. glomerata* occurred by interaction with gamma amino butyric acid (GABA_A) receptors (Table 4). An increase in the concentration of GABA results in the inhibition of glutamine, aspartate, and glutamate, directly linked to increased behavioral and anxiety effects [52]. The study, therefore, suggests that the anxiolytic effect of *M. glomerata* in mice is because of increased concentrations of GABA and decreased levels of glutamate in the hippocampus [55]. Present studies indicated that *M. glomerata* exhibits a low toxicity profile [51, 56, 58].

In a recent clinical trial, the toxicity of guaco was evaluated for safety and the results suggested that the medicinal plant is safe at the concentrations and dose regimen tested [57]. Earlier toxicological evaluations reported conflicting views on the toxicity of guaco extracts. In their study, Graca et al. [133] reported that no toxicity was seen with guaco extracts; however, Leite et al. [134] and Dos Santos et al. [135] suggested DNA and anticoagulant damage by guaco extracts. The in vivo and in vitro models utilized for the studies failed to reflect secondary metabolites ability to undergo biotransformation after oral administration in humans [136]. The reported low toxicity of *M. glomerata*, the antidepressant, and the anxiolytic activities make the plant a potential candidate for managing depression, substance use disorders, and other mental health challenges in LAC. Presently, guaco is officially on the list of the Brazilian healthcare system, and the syrup is marketed for respiratory tract disorders [59].

3.1.5 *Matricaria recutita* L. (chamomile) [Asteraceae]

Matricaria recutita (Chamomile) is a centuries-old herb used traditionally to treat various illnesses. The herb has been used in Egypt, Rome, Greece, and many parts of the world from ancient times as herbal remedy for wounds, spasm, inflammation, and as an antiseptic in addition to its nutritional and cosmetic benefits [70]. *M. recutita* herb promotes a calming effect and is helpful for anxiety, sleeplessness, gastrointestinal tract disorders such as diarrhea and gas, and topical application in cancer and mouth sores management (Table 1). Presently, 26 countries have included *M. recutita* in their pharmacopeia reported for its antispasmodic, anti-inflammatory, neuroprotective, chemopreventive, antioxidant, antipruritic, chemopreventive, antimicrobial, antiparasitic, antiplatelet, antidiarrheal, anxiolytic, and wound healing activities [60, 61, 70]. The major bioactive compounds of chamomile include coumarins, flavonoids, phenolic acids, and essential oil that has been approved by FDA for cosmetics and food (Table 3) [70]. The central nervous effects of

chamomile have been evaluated clinically against depression, sleep-deficiency, Alzheimer's disease, and anxiety disorders [71].

Preliminary preclinical and clinical studies suggest that persons with generalized anxiety disorders may benefit from *M. recutita* dietary supplements [60]. However, little is known about chamomile's health effects because there are few studies on chamomile in people for individual conditions. The potential of *M. recutita* to reduce anxiety has been reported in South America [62]. The ability of *M. recutita* to improve sleep problems and reduce depression and boredom in postpartum women, thereby enhancing sleep quality, was also reported in a randomized experimental study [63]. In an earlier mice model hole-board test, Kesmati et al. [64] demonstrated that the anxiolytic effects exhibited by *M. recutita* might be associated with GABA_A receptors activity in the central nervous system due to the plant's rich bioactive flavonoids. Current literature suggests that the mechanism of action of *M. recutita* is expressed through noradrenaline, dopamine, serotonin, and GABA neurotransmission in the central nervous system (Table 4). In addition, its indirect action on the vasomotor and the HPA has been denoted [65]. Most recently, the anxiolytic and antidepressant activity of *M. recutita* was shown to produce significant clinical antidepressant and anxiolytic effects in a randomized, double-blind, placebo-controlled trial [66]. *M. recutita*'s ability to scavenge free radicals makes it a potentially effective medicinal plant for the treatment of cerebral ischemia, Alzheimer's disease, Parkinson's disease, neurological, and possibly substance use disorders [67–69].

3.1.6 *Passiflora caerulea* L. (flor de passion) [Passifloraceae]

Widely distributed in the continent of South and Central America, *Passiflora caerulea* (maracujá-laranja, flor de passion, mburucuyá) has been traditionally used as a sedative, antistress, anxiolytic, and for nutritional, flavoring, and a sweetener [72]. Although the British, Brazilian, and European pharmacopeias consider the Argentine *P. caerulea* as a potential adulterant of *P. edulis* and *P. incarnata*, the alkaloids of hamala found in *P. caerulea* are reported to be the major contributor to the plant antistress and anxiolytic activities [73, 74]. In addition, Passiflora has been reported in the management of morphine dependence, neurotic disorders, neuralgia, convulsions, hemorrhoids, painful menstruation, insomnia, diarrhea, antispasmodic, and anthelmintic (Table 1) [74, 75]. The primary bioactive compounds found in Passiflora include cyanogenic glycosides, flavonoids, phenolic compounds, and alkaloids [β -carbolines] (Table 3) [58]. Animal studies on mice demonstrated that aqueous and ethanolic extracts of the leaves of *P. caerulea* L. had significant

anticonvulsant, analgesic, antioxidant, anti-inflammatory, and antipyretic activities [75]. Although the mechanism of action of the chemical composition of *Passiflora* is still being studied, most studies suggest that the anxiolytic activity of the plant is linked to the neurotransmitter GABA (Table 3). The flavonoids found in *Passiflora* are related to the modulation of the GABAergic system, where they bind to the benzodiazepine binding ligand of GABA receptors demonstrating antianxiolytic effects (Table 4) [76].

Relatedly, chronic substance use has been reported to induce oxidative stress and neuroinflammation, in the process, exacerbating addiction-related neural damage. Bioactive compounds like quescetin and flavonoids found in *passiflora* species protect against neurodegeneration by decreasing oxidative markers and pro-inflammatory cytokines such as IL-6 and TNF- α . Improved cognitive function in withdrawal models has been linked to the anti-inflammatory effects of *P. incarnate* [137]. Furthermore, *Passiflora* species have demonstrated neuroprotection and synaptic plasticity in neural repair, countering substance-induced synaptic atrophy through enhanced serotonin and GABA signaling [80]. While paucity of information exists from direct studies on the utilization of *P. caerulea* in the management of SUD, related species (*P. incarnate*) has shown promising potential in benzodiazepines tapering. Reduced cravings and hyperexcitability have been reported in alcohol withdrawal via GABA modulation in preclinical studies [80]. Also *P. incarnata* facilitated benzodiazepine reduction through GABAergic synergy with no dependency or rebound effects when given as an adjuvant therapy [79].

A recent study on *P. caerulea* validated its neuroprotective, antispasmodic, antidiabetic properties, highlighting that limited studies exist on its long-term toxicity [138]. While studies on *P. caerulea* as a potential for SUD management are limited, related species like *P. incarnate* provide indirect insights into its potential mechanism of action in addressing SUD in LAC. Through GABA receptor modulation, *Passiflora* species (including *P. incarnate*) exert sedative and anxiolytic effects on the central nervous system (Table 4). With a lower risk of dependence, flavonoids like chrysin and apigenin mimic benzodiazepines by binding to GABA_A and GABA_B to enhance GABAergic neurotransmission [139]. By mitigating withdrawal symptoms through GABAergic activity, *P. incarnate* extracts decreased benzodiazepines dependence in clinical trials, suggesting a similar pathway for *P. caerulea* [74]. Furthermore, increase in the levels of norepinephrine, dopamine, and serotonin through the inhibition of monoamine oxidase (MAO) enzymes by the indole alkaloids (harmine and harman) found in *passiflora* has been reported to counteract cravings and dysphoria linked to

substance withdrawal. Inhibition of MAO may prevent relapse risk for SUD and stabilize mood, particularly for opioids and stimulants use disorders [74].

Previously, *Passiflora* was reported to activate the cholinergic neurotransmission pathway similar to diazepam in a dose-dependent fashion, improved cognitive function, had anticonvulsant activity, and significantly reduced oxidative damage [77]. These findings strongly suggest that *Passiflora* has the potential for the management of neurodegenerative diseases and epilepsy. Presently *Passiflora* is listed in some selected monographs, including that of the World Health Organization (WHO), Brazil, the UK, the USA, and the European Union [58]. The sedative, anticonvulsive, antianxiolytic, and low toxicity effects of *Passiflora* make it a potential medicinal plant for managing SUD and other central nervous system disorders in LAC. Necessitated targeted studies specifically on *P. caerulea*'s flavonoid and alkaloid composition is critical, considering that phytochemical profiles differ across *Passiflora* species.

3.1.7 *Piper methysticum* L. f. (Kava) [Piperaceae]

Piper methysticum, known as kava, has been used for therapeutic and recreational purposes. Although native to the Pacific Island region, *P. methysticum* is now naturalized and cultivated in the Americas [78]. The root extract is used as a remedy for gonorrhea, bronchitis, rheumatism, inflammation, and other respiratory diseases. *P. methysticum* is traditionally used to ameliorate stress and anxiety and is sometimes paired with alcohol for recreational use (Table 1). The active ingredients are a group of bioactive compounds known as kava lactones, which have significant analgesic and anesthetic effects via the non-opiate pathways [81]. Presently, *P. methysticum* is sold as an herbal dietary supplement in the USA [78].

Due to its multi-target ethnopharmacological effects on stress pathways and neurotransmitter systems, *Piper methysticum* (kava) has generated attention for its potential role on managing SUD. Unlike benzodiazepines, the primary bioactive compounds in kava (kavalactones), modulates GABA_A receptors by increasing the number of GABA binding sites rather than directly binding to receptors (Table 4). This GABAergic neurotransmission leads to reduction in anxiety and withdrawal symptoms without causing dependency or impairing cognition [86, 140]. Kava's ability to modulate GABA_A is critical for alleviating hyperexcitability and anxiety [84, 85]. Also, at the synapses, kavalactones particularly yangonin, increases norepinephrine, serotonin, and dopamine levels by reversibly inhibiting MAO-B [86, 140]. Cravings and dysphoria associated with substance withdrawal can be counteracted by elevated monoamines, making kava a potential candidate for managing opioid, stimulants,

and other substances of addiction in LAC. Additionally, kavalactones enhances noradrenergic signaling in the prefrontal cortex by inhibiting neuronal norepinephrine reuptake, while potentially mitigating reward-seeking behaviors via modulating dopamine release [86]. These multiple actions of improved attention processing coupled with GABAergic relaxation may stabilize mood and decrease impulsivity in SUD patients.

Extensive clinical studies of *P. methysticum* have shown that the plant extracts are as effective as benzodiazepines in stress and anxiety management. In addition, *P. methysticum* did not impair mental capability or alertness, nor did it show evidence of psychological or physical dependence with a very low incidence of reported problematic side effects [82, 83]. In addition, *P. methysticum* does not contain alcohol, and its relaxant effects are due to the lipid-soluble psychoactive kavalactones reported to have analgesic, anxiolytic, sedative, hypnotic, antithrombotic, and muscle relaxant effects [84, 85]. In a recent preclinical studies, Volgin et al. [86] suggest that kava's neuroprotective effects in the cortical and hippocampal regions supports cognitive recovery during substance use abstinence. Kava may protect against oxidative stress and neuroinflammation induced by chronic substance use via glutamate excitotoxicity attenuation. N-Methyl-D-aspartate (NMDA) receptors implicated in addiction-related synaptic plasticity are modulated by kavalactones to produce these effects [140]. Finally, kavalactones (at high concentrations) bind to opioid receptors in the brain to produce analgesia mediated by the blockade of calcium and sodium, a non-opioid pathway. This indirect non-opiate analgesic pathway could decrease the over reliance on opioid pain medications thereby indirectly addressing opioid use disorder [141].

In traditional usage, *P. methysticum* is generally safe, non-addictive, and non-hallucinogenic and has long been suggested as an alternative to benzodiazepines in controlling generalized anxiety disorder alternative primarily since it is not known to trigger any serious health concerns [84]. Its ability to enhance GABA_A activity and decrease other neurotransmitters in the central nervous system is essential attributes that make *P. methysticum* a potential alternative in managing SUD in Latin America and the Caribbean, mainly because the approved herbal supplements can be easily accessed from the USA. Henceforth, further studies for the use of kava for SUD should be intensified specially to unravel the exact mechanism of individual kavalactones such as kavain and methysticin in association to SUD management. Most data derived for kava were from anxiety studies limiting direct evidence in SUD populations. Finally, due to kava's ability to inhibit liver enzymes (cytochrome P450) caution is required with concurrent polypharmacy [141].

At the moment, hepatotoxicity remains a safety concern with kava linked to excessive dosing or poor-quality extracts. However, better safety profiles with noble kava varieties like acetone extracts have been reported [141].

3.1.8 *Rhodiola rosea* L. (golden root) [Crassulaceae]

Rhodiola rosea has several bioactive compounds, including gallic acid derivatives, proanthocyanins, monoterpene alcohols, flavonolignans, flavonoids, phenylethanoids, aryl glycosides, phenylpropanoids, and cyanogenic glycosides (Table 1). Preclinical and clinical studies have reported *R. rosea* to possess central nervous system stimulation, anxiolytic, antidepressant, antifatigue, cardioprotective, neuroprotective, lifespan increasing, and adaptogenic effects [87, 88]. Adaptogens, such as *Rhodiola rosea*, are a class of non-toxic herbal substances that promote homeostasis and modulate neuroendocrine immune system to enhance the body's psychological, chemical, and physical resilience to stress [142, 143]. The ability for adaptogens to mitigate stress-related damage and enable organisms to adapt to stressors through their ability to induce a state of "non-specific resistance" (SNSR) has been scientifically documented even though the concept is rooted deeply in traditional medicines and Ayurveda (Table 4) [143, 144].

At present, direct studies on *R. rosea* in SUD management are limited. However, emerging preclinical and clinical evidence highlights its neuropharmacological and adaptogenic properties, which may address key pathways implicated in substance addiction. First, salidroside, a primary bioactive compound found in *R. rosea*, modulates the monoaminergic systems (norepinephrine, serotonin, and dopamine) critical in withdrawal symptoms and reward processing. The inhibition of MAO by salidroside increases synaptic dopamine levels and potentially decrease dysphoria and cravings associated with substance withdrawal [91, 124]. Second, by enhancing serotonin signaling, *R. rosea* may mitigate anxiety and stabilize mood during substance use recovery [65, 89]. Third, the hypothalamic-pituitary-adrenal (HPA) axis is disrupted by chronic substance use, exacerbating stress-related relapse in patients with substance dependence. As an adaptogen, *R. rosea* reduces oxidative stress and normalize cortisol levels markers linked to HPA hyperactivity [65, 89]. Stress-induced behaviors were attenuated by *R. rosea* extracts in animal models by modulating FOXO/DAF and Hsp70 (heat shock proteins) pathways thereby enhancing stress resilience [87].

Fourth, because neuronal damage through apoptosis and oxidative stress are induced by chronic substance use, tyrosol and salidroside (*R. rosea* bioactive compounds) have antioxidant properties that protect against ROS overproduction and mitochondrial

dysfunction. In a recent systematic review, Li et al. [145] reported that preclinical studies demonstrate *R. rosea*'s ability to reduce caspase-3 activity and upregulate antiapoptotic proteins (Bcl-2) thereby preserving neuronal viability in neurotoxicity and ischemia models, suggesting that these mechanisms may counteract neurodegeneration in chronic substance use. Fifth, oxidative stress and pro-inflammatory cytokines IL-6 and TNF- α elevated in addicted populations can be reduced by *R. rosea*. Studies have indicated that lipid peroxidation and NF-kB signaling are suppressed by salidroside thereby mitigating the neuroinflammation linked to alcohol and opioid use disorders [91, 124]. In a recent meta-analysis on *R. rosea*, ischemic stroke models indicated its capacity to lower brain edema and TNF- α , suggesting a broader anti-inflammatory application [145]. Furthermore, preclinical and clinical evidence of *R. rosea* use in cognitive enhancement, anxiety, and depression shows mild-to-moderate alleviation of anxiety and depression, comorbidities common in SUD [65, 89]. In addition, *R. rosea* enhances mental stamina and improves focus under stress, potentially aiding cognitive rehabilitation in substance use recovery. Also, by reducing cortisol levels and enhancing the synthesis of ATP, *R. rosea* counters fatigue, a relapse [87, 146].

In a 2-week study to evaluate self-reported cognition, stress, anxiety, and other mood symptoms among 80 mildly anxious participants, *R. rosea* experimental participants reported a significant reduction in depression, confusion, anger, stress, and anxiety, demonstrating notable improvement in total mood [89]. In an earlier related study, Cayer et al. [90] reported a dose-dependent moderate effect in the higher-anxiety social interaction test and anxiolytic activity in the elevated plus maze and conditioned emotional response test. The study further suggested that other pathways may be involved in the mechanism of action of *R. rosea* due to the low anxiolytic effect demonstrated by the extract in an in vitro GABA_A benzodiazepine receptor binding assay [90]. The advantageous effects of *R. rosea* to mediate monoamine oxidase, cortisol, nitric oxide, c-Jun N-terminal protein kinase 1 (JNK1), and JNK-mediated effects on glucocorticoid receptors [87] are potential benefits for the treatment of SUD in LAC more so that the traditional acceptability and uses for other health conditions make it attractive as a safe alternative in SUDs within LAC.

Although, presently, a direct evidence of *R. rosea* in the management of SUD in LAC is non-existent. The submissions provided in this review were essentially extrapolated from stress and depression models, key pathways in SUD management [87, 147]. Bioactive variability of extract composition may necessitate the need to standardize formulations [91, 124]. While generally

well-tolerated, *R. rosea*'s interaction with selective serotonin reuptake inhibitors calls for the need for caution [87, 148].

3.1.9 *Scutellaria lateriflora* L. (skullcap) [Lamiaceae]

Traditionally native Americans have used *Scutellaria lateriflora* to treat kidney, digestive, central nervous systems, and menstrual disorders [92]. Also, chorea, insomnia, epilepsy, nervous tension, and hysteria are central nervous system disorders managed traditionally by *S. lateriflora* (Table 1) [92]. Presently, the aerial part of the plant, rich in bioactive flavonoids such as baicalein, wogonin, baicalin, and scutellarin are used for their antispasmodic, sedative, and tranquilizing activities (Table 3) [92, 93]. The flavonoid activity on the central nervous system has been attributed to be similar to benzodiazepines, where they modulate GABA to produce sedation [94]. The ability of some of the bioactive compounds in *S. lateriflora* to produce sedation is a useful mechanism reported in animal studies that can also treat SUDs. Brock et al. [149] reported a significantly enhanced global mood in randomized healthy participants with no reduced cognition or energy when treated with *S. lateriflora*. In a recent review, Shah et al. [94] summarized the biopotentials of *S. lateriflora* to include a diverse range of significant pharmacological activities such as analgesics, antiangiogenic, anti-inflammatory, enzyme inhibition, antifeedant, antioxidant, and antimicrobial properties (Table 1).

Although presently *S. lateriflora* has not been directly studied in the context of SUD, its ethnopharmacological effects on neuroprotection and the neurotransmitter systems in the brain suggest significant therapeutic relevance for SUD management. Flavonoids like wogonin and baicalin found in *S. lateriflora* enhances inhibitory signaling and neuronal excitability by binding to the BZD site of GABA_A receptors [150, 151]. Withdrawal symptoms like seizure, anxiety associated with substance dependence, particularly BZD or alcohol withdrawal are effectively managed by GABAergic activity [150, 151]. Also, reduction in anxiety-like behaviors in open-field and plus maze test in preclinical studies among rodents suggest *S. lateriflora*'s ability in alleviating stress-related cravings [130, 149]. Additionally, ikonnikoside and scutellarin (flavonoids of skullcap) modulate serotonin 5-HT₇ receptor pathways to influence reward circuitry and influence mood stabilization, which are largely dysregulated in SUD [150, 152]. Skullcap's mood-enhancing effects without cognitive impairment were reported in a human crossover trial, highlighting its potential to address comorbid depression in SUD [149, 151]. Also, the flavonoids (baicalin) of Skullcap exhibit neuroprotective effects by reducing inflammation and oxidative

stress implicated in neurotoxicity from chronic drug use. Furthermore, baicalin and other *Scutellaria* species mitigates neuronal damage in cerebral ischemia models and improve cognitive function in cerebral ischemia and Alzheimer's [151]. These properties of *Scutellaria* may support recovery in SUD, particularly in stimulant-induced neurodegeneration and opioid dependence [151]. In earlier rodent model studies, Zhang et al. [93] reported anti-convulsant effects of skullcap against seizures induced by pentylenetetrazol and pilocarpine, likely via glutamate and GABAergic modulation. This modulation could be relevant for managing withdrawal-related seizures in barbiturate or alcohol dependence.

Some *Scutellaria* species have been reported to produce adverse effects with prolonged usage. Although hepatotoxicity has been reported with *S. lateriflora*, studies have suggested that adulteration with other hepatotoxic plants (*T. chamaedrys*, *T. Teucrium*) rather than *S. lateriflora* may have been the source of hepatotoxic events [153, 154]. Safety studies and monitoring for hepatotoxicity of *S. lateriflora* still remain critical. A significant concern in the use of medicinal plants is adulteration with other plants hence the need to ensure purity of products to avoid interactions and toxicity. The lack of ease of access by many communities to healthcare services, the high cost of Western conventional medicines, and the abundance of medicinal plants in LAC provide an incentive to explore *S. lateriflora* and other beneficial ethnomedicinal plants in SUD treatment in the region, primarily since most of the plants have been used traditionally and culturally with proven effectiveness. Although currently no direct clinical trials on *S. lateriflora* for SUD exist, current evidence for this review is derived from preclinical studies on neuroprotection and anxiety, necessitating the need for further research. Future research should prioritize clinical trials in substance dependence populations, focusing on neurodegeneration and withdrawal symptom. While Skullcap shows potential through neuroprotection, serotonergic, and GABAergic mechanisms, a direct evidence for its use on SUD applications is lacking, and hence the need for further studies in this area.

3.1.10 *Leonotis nepetifolia* (L.) R.Br. (dagga, klip, lion's ear, cordão-de-frade') [Lamiaceae]

Leonotis nepetifolia originally indigenous medicinal plant from the African continent has now spread to many tropical regions of the world including Latin America and the Caribbean with emerging relevance as a potential therapy for SUD. Presently, the plant is integrated into many complementary systems indirectly linked to SUD. *L. nepetifolia* is used as a traditional medicinal therapy for common comorbidities in withdrawal and addiction such as in pain, seizures, and anxiety disorders. In an

earlier ethnobotanical survey of the plant, Clement et al. [97] reported its traditional use in Trinidad for cough and fever even though a direct link with SUD applications remain understudied (Table 2). However, its traditional use to manage stress-related symptoms aligns with broader regional practices, which present critical potentials in SUD management [95, 101]. Therapeutic potentials of *L. nepetifolia* have been attributed to its rich bioactive compounds such as phytosterol and terpenoids, which modulate central nervous system neurotransmitters [98, 99]. Also, flavonoids such as glycosides, luteolin, and apigenin with neuroprotective and antioxidant activities are significant bioactive compounds found in the plant with potentials for SUD management (Table 3) [95]. Additionally, neuroprotective and anti-inflammatory effects linked to verbascoside, a phenylpropanoid glycoside extracted from the flower provide significant opportunity for exploration in SUD therapy [96]. These bioactive compounds found in *L. nepetifolia* collectively contribute to its anti-inflammatory, anticonvulsant, and anxiolytic actions [100, 101]. Pharmacological actions such as reduction in stress behaviors, GABAergic modulations, antioxidant, anti-inflammatory, and neuroprotection effects reported in *L. nepetifolia* are critical in SUD management.

The methanol extract of *L. nepetifolia* (150 mg/kg) mimicked diazepam's anxiolytic effects by decreasing rearing behavior in mice, an important reduction in stress behavior is beneficial for SUD management [100]. In the same study, GABAergic modulation was suggested where *L. nepetifolia* methanol extracts stems prolonged diazepam-induced sleep in mice possibly on GABA A receptors, a key pathway for withdrawal and anxiety management. Furthermore, luteolin mitigation of oxidative stress, a contributor to neurotoxicity in chronic substance use, was reported, while the plants extract enhanced cellular antioxidant defenses and inhibition of lipid peroxidation, protecting against opioid- or alcohol-induced neuronal damage [99, 101]. Finally, the hexane fractions of *L. nepetifolia* reduced TNF- α pro-inflammation cytokines in macrophages, a key activity to addressing neuroinflammation associated with substance use disorders [101,102].

While in traditional medicinal plant doses, *L. nepetifolia* is regarded as generally safe, a recent study highlighted teratogenic effects in zebrafish embryos with ethyl acetate fractions of the flowers at a high concentration of IC₅₀:57.70 μ g/ml [96]. Although pure extracts of the plant showed low cytotoxicity in murine models, limited data suggest improper preparation or adulteration may pose adverse potentials [101]. In dose-dependence studies in mice, the intraperitoneal LD₅₀ was 3.8 g/kg, indicating safety at lower doses [100]. With the present

information, the multifaceted anti-inflammatory, antioxidant, and GABAergic mechanisms of *L. nepetifolia* significantly align with therapeutic targets for substance use disorder management. While currently safety profiling and clinical validation are critical for its integration into evidence-based addiction care, preclinical evidence supports GABAergic modulation, human trials are needed to confirm these effects for SUD management.

3.1.11 *Turnera diffusa* Willd. ex Schult, (Damiana) [Turneraceae]

Turnera diffusa is a Native American and Caribbean shrub used traditionally for its aphrodisiac, anxiolytic, antianemic, antidiabetic, laxative, abortifacient, antipyretic, and antidepressant effects (Table 1). *T. diffusa* is rich in albuminoids, α -copaene, α -pinene, arbutin, barterin, β -pinene, β -sitosterol, calamenene, caoutchouc, chlorophyll, 1,8-cineole, cymene, cymol, damianin, essential oil, gamma-cadinene, gonzalitosin-i, hexacosanol-1, luteolin, quinovopyranosides, tannins, tetraphyllin b, thymol, triacontane, and trimethoxyflavones (Table 3) [102]. Several flavonoids from plants are inhibitors of monoamine oxidases (MAO), and phytochemical studies have revealed that *T. diffusa* contains flavonoids, cyanogenic glycosides, terpenoids, and other secondary metabolites [103].

In a comprehensive review, Szewczyk and Zidorn [104] summarized the various reported beneficial uses of *T. diffusa* in the Americas to include diuretic, asthma, cough, importance, influenza, skin and gastrointestinal disorders, and to promote ovulation. *T. diffusa* was allegedly considered one of the essential traditional medicinal plants of the ancient Mayas. *T. diffusa* was previously reported for its adaptogenic effects in mice administered 10–1000 mg/kg hydroalcoholic extract orally with no acute toxicity seen in the mice [105]. The study further reported the absence of stimulant, neurotoxic, and depressant effects with *T. diffusa* due to the absence of motor coordination, locomotor activity, or time pentobarbital-induced sleep. The significant antianxiety effects of *T. diffusa* have been suggested as a viable alternative to benzodiazepines with methanol extracts orally administered to mice [106, 107]. Both methanol and aqueous extracts of *T. diffusa* demonstrated significant activity in mice at a dose of 2 mg/kg using the mirrored chamber test, light/dark test, and raised plus maze model [108, 109]. Pure apigenin was also reported to show antianxiety activity [102].

With these multifaceted ethnopharmacological benefits, *T. diffusa* presently shows promising potential for SUD management through stress reduction, neuroprotection, and neurotransmitter modulation.

Hypothalamic–pituitary–adrenal (HPA) axis dysregulation and chronic stress response are closely linked to substance use disorders (Table 4). The adaptogenic properties of *T. diffusa* has been reported to possibly decrease cortisol levels and modulate stress responses, potentially reducing relapse risks in SUD [155, 156]. Although direct evidence for *T. diffusa* in SUD is needed, animal studies on related plant species highlights reduced stress-induced behaviors [110]. Also, IL-6 and TNF- α pro-inflammatory cytokines elevated in substance-induced neuroinflammation can be suppressed by terpenoids found in *T. diffusa*. The traditional use of *T. diffusa* for libido enhancement suggests indirect effects of the medicinal plant on the estrogen and dopamine pathways, which are significant in reward processing, a potential activity for SUD management [110, 155, 156]. In addition, terpenoids and flavonoids (quercetin and kaempferol) of *T. diffusa* decrease depressive and anxiety symptoms associated with substance withdrawal. GABAergic effects of quercetin alleviate seizures and anxiety during BZD and alcohol withdrawal [155].

Similarly, binding to serotonin 5-HT receptors by *T. diffusa* demonstrates potential mood stabilizing effects while decreasing cravings linked to reward pathways [156, 157]. Furthermore, the antioxidant and neuroprotective activities of *T. diffusa* have been reported to protect neuronal cells and mitigate oxidative damage [110]. Since chronic substance use contributes to neurodegeneration by inducing neuroinflammation and oxidative stress, the likelihood to inhibit inflammation and lipid peroxidation due to the protective effects against neurotoxicity in cell models by extracts of *T. diffusa*, is a promising activity for SUD management. Finally, prolonging the effects of catecholamines (serotonin and dopamine) in activity reward circuits through inhibition of MAO has been reported by the extracts of damiana, key pathway for SUD withdrawal symptoms mitigation [110].

Although currently no human trials directly address *T. diffusa* in the management of SUD, evidence relies on preclinical models and traditional use of the medicinal plant where it demonstrates promising activity on stress reduction, neuroprotection, and neurotransmitter modulation [104]. Potential adverse effects of *T. diffusa* include headaches and nausea, and although hepatotoxicity is rare but not impossible with adulterated products. Damiana interacts with antihypertensive and sedatives. These findings strongly support traditional claims of the medicinal plant and are significant for the LAC region as *T. diffusa* showed evidence in animal studies as a promising agent as an anxiolytic

and, by extension, for consideration in the treatment of SUDs.

3.1.12 *Zingiber officinale* var. *officinale*, (ginger) [Zingiberaceae]

Zingiber officinale (ginger) is a common shrub used both as a spice and for many ailments. *Z. officinale* has antioxidant, anti-inflammatory, and antinociceptive properties, and it is documented that major bioactive constituents are gingerols, shogaols, paradols, and zingerone (Table 1).

Although current hypotheses and evidence of the use of *Z. officinale* have not been directly studied in the management of SUD, its documented ethnopharmacological and bioactive properties like neuroprotection, antioxidant, and anti-inflammatory activities suggest therapeutic applicability for the restoration of equilibrium in SUD management [111]. The plant's antiaddictive effects may be mediated through its anti-inflammatory and antioxidant properties on neuroinflammation and its ability to reduce morphine glial activation [112]. For instance, zingerone, shogaols, and gingerols are primary bioactive compounds of the plant that activate Nrf2 signaling pathway to produce potent antioxidant effects leading to cellular defense against oxidative stress (Table 3) [119, 121]. Inhibition of IL-6 and TNF- α (pro-inflammatory cytokines) and the reduction of lipid peroxidation via the suppression of Akt and NF- κ B pathways by ginger may mitigate neuroinflammation and oxidative damage induced by chronic substance use, thereby minimizing addiction relapse and neuronal death (Table 4) [121, 122, 158]. Furthermore, supplements of *Z. officinale* were reported to decrease the levels of pro-inflammatory cytokines TNF- α and IL-6, reduce lipid and protein oxidation, and increase antioxidant indicators [114]. Because alterations in the levels of oxidized low-density lipoprotein (Ox-LDL), nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), and 8-hydroxy-2'-deoxyguanosine as a result of alcohol exposure can lead to oxidative stress, the antioxidant effects of *Z. officinale* are beneficial in alcohol addiction therapy [111, 114].

Moreover, the neuroprotective properties of *Z. officinale*, such as improvement of the histological features of the brain, reducing apoptosis, inflammation, oxidative stress, modulation of astroglial response to injury, decreased acetylcholine expression and the levels of malondialdehyde (MDA), improved neurogenesis, and acceleration of the brain-oxidant defense mechanism have been reported due its antioxidant properties [115–117]. Recently, Deng et al. [158] reported the reversal of ethanol-induced oxidative brain damage in animal models suggesting ginger's neuroprotective potentials in alcohol use disorders. Similarly, ginger's anti-inflammatory properties significantly decrease the

neuroinflammation linked to substance-induced neurodegeneration (Table 3). Its bioactive compounds prolong dopamine activity in reward pathways through the inhibition of MAO enzymes, thereby modulating serotonin and dopamine [119, 120]. Reducing apoptosis in the hippocampal neurons exposed to neurotoxins and restoring synaptic plasticity have been reported in preclinical studies [118, 158]. Relatedly, ginger has been reported to reduce inflammation and pain via prostaglandin and COX-2 synthesis signifying its ability to alleviate substance withdrawal-related discomfort [119, 120]. Ginger's efficacy in reducing postoperative nausea in clinical trials has been noted in recent meta-analyses, suggesting potential utility in managing nausea and vomiting associated with alcohol or opioid withdrawal symptoms [120, 158].

Emerging evidence suggest ginger's ability to restore microbial balance via the modulation of gut-muscle axis [118]. ZOPA-1 polysaccharide found in ginger enhances short-chain fatty acid production and gut microbiota diversity, which influence stress response and brain function. Since increased susceptibility to withdrawal symptoms and addiction is associated with dysregulated gut microbiota, improving metabolic waste clearance and reducing systemic inflammation by ginger's ability to restore microbial balance may indirectly support SUD management [118, 159]. Conversely, *Z. officinale*'s antioxidant properties have been suggested to attenuate alcohol-induced nephron toxicity [113].

Direct clinical trials to specifically address the use and efficacy of ginger in SUD management is presently lacking. The review's current data are deduced from studies on neurodegeneration, pain, and inflammation [120, 160]. While ginger is generally considered safe and has very low toxicity in pregnant and non-pregnant animal studies, high doses may interact with antihypertensive or anticoagulant medications [161]. Hence, dried or fresh ginger formulations may have variabilities that affects the concentrations of the bioactive compounds complicating dose–response analysis requiring the need for standardization [119, 159]. For SUD and addiction contexts, translational research is urgently needed to validate the efficacy of ginger, while prioritizing clinical trials among substance dependence populations using standardized *Z. officinale* formulations. The safety of *Z. officinale*, coupled with its vast therapeutic benefits and rich abundance in LAC, makes the plant a suitable target for managing SUD in the region.

4 Sociocultural contexts of plant-based therapies in LAC for SUD

In Latin America and the Caribbean, SUD management using plant-based therapies by therapeutic communities is deeply rooted in evolving public health strategies, intergenerational practices, and cultural traditions. These therapies are shaped by grassroots advocacy, historical contexts, and cultural resilience, and their therapeutic potentials are progressively acknowledged, thereby bridging evidence-based policies with traditional practices [9, 162]. Table 5 highlights the interplay of cultural, policy, and institutional factors shaping plant-based SUD therapies in LAC.

4.1 Traditional medicine and cultural heritage in LAC therapeutic communities

Often intertwined with Afro-descendants and indigenous healing rituals, plant-based therapies like ibogaine and ayahuasca reflect centuries-old practices. For instance, the emphasis on collective communal healing and spiritual purification by the Amazonian communities aligns with deep cultural narratives of balance restoration between the environment and the individual [162, 163]. Presently, many therapeutic communities such, as the Takiwasi Center in Peru, are increasingly incorporating these traditional practices as a core component of addiction treatment, which blends psychotherapy with shamanic practices to address addiction issues within the community [162]. Similarly, in LAC countries like Chile and Peru, horticultural therapy programs incorporate traditional gardening practices to foster psychological

and emotional recovery in patients with substance use disorders reflecting the fusion of ancestral wisdom and therapeutic framework [164].

4.2 Stigma and barriers to conventional treatment in LAC communities

Due to cultural stigma, distrust, or fears of judgment with conventional medical systems, many individuals in LAC communities avoid institutionalized treatments, creating a significant barrier to SUD and mental health treatments [165]. Traditional plant-based therapies accepted within a community help to develop community trust and minimize the stigma often faced by marginalized populations accessing conventional medicines for the management of SUD in LAC. Medicinal plants and other complementary therapies embedded in cultural frameworks are less institutionalized and perceived as more acceptable by the populations within a community. For instance, more interest in medicinal traditional remedies like *P. incarnate* (passion flower) is observed for anxiety relief during withdrawal in Puerto Rican communities with high opioid misuse rates, fostering trust through culturally familiar practices [9, 166]. These favored, less stigmatizing, and perceived culturally congruent traditional interventions bypass institutionalized barriers, leveraging traditional knowledge for mental health and SUD management.

Table 5 Sociocultural contexts of plant-based therapies in LAC for SUD

Aspect	Key points	References
Traditional medicine and cultural heritage	Plant-based therapies (e.g., ayahuasca, ibogaine) are deeply rooted in indigenous and Afro-descendant healing rituals Takiwasi Center (Peru) combines Amazonian traditional medicine with Western psychotherapy Horticultural therapy programs in Chile/Peru integrate ancestral gardening practices	[9, 162–164]
Stigma and barriers to conventional treatment	Stigma and distrust of institutionalized healthcare drive preference for culturally congruent plant-based therapies Medicinal plants like <i>Passiflora incarnata</i> are used in Puerto Rican communities to reduce anxiety during withdrawal, fostering trust	[9, 165, 166]
Cultural identity and acculturation dynamics	Acculturation to Western norms increases SUD risk; cultural preservation (e.g., familismo) acts as a protective factor Rituals with plants like <i>Salvia divinorum</i> in Guatemala/Mexico emphasize ancestral reconnection to counter addiction-related isolation	[162, 165, 167]
Policy and integrative initiatives	PAHO/WHO projects aim to improve SUD policies but face challenges in formal recognition of traditional practices Colombia lacks legal recognition for <i>Banisteriopsis caapi</i> ; Chile's 2024 policy integrates therapeutic gardens into rehabilitation	[9, 162, 164]
Collaborations and regional cooperation	International collaborations (UNODC, CICAD, RIOD) support PAHO's regional efforts Regulatory harmonization (AMLAC, CRS) seeks to streamline approvals but focuses mainly on conventional medicines	[9, 168, 169]

4.3 Cultural identity and acculturation dynamics

Attrition of traditional values and acculturation to Western norms have been linked to increased risk of substance use disorders in many LAC populations. Also, studies highlight that the retention of culture and strong family bonds (familism) act as factors that prevent substance misuse [165, 167]. Systematic oppression and historical trauma from colonialism influence significantly contribute to acculturation that leads to substance use patterns in the region (Table 5).

For instance, lower rates of SUD in Latinx immigrants in the USA with low acculturation to Western lifestyles were reported compared to assimilated or bicultural peers, underscoring cultural preservation in resilience [165, 167]. Contrariwise, heightened vulnerability to substance initiation due to identity conflicts and social pressures was reported in youths navigating dual cultural identities [165]. Increasingly, in many LAC communities, today plant-based therapies (alone or in combination with other practices) are framed as tools for addressing these wounds. For example, Guatemalan and Mexican communities perform rituals involving *Salvia divinorum* Epling and *Játiva* or kratom to emphasize ancestral reconnection and communal support, in the process, countering the isolation linked to dependence and addiction [162, 166].

4.4 Policy and emerging integrative initiatives

While current initiatives to strengthen public health responses to substance use disorders in LAC are applauded, limited formal recognition of medicinal plants for SUDs still exists in the region. The establishment of PAHO's Universal Care for Substance Use Disorders provides a framework for tackling the issue of SUD in LAC. However, traditional practices often clash with regulatory frameworks, which significantly impact public health. In Colombia, for instance, despite its deep cultural significance and traditional use, *B. caapi* is still not legally recognized, limiting its impact as a therapeutic agent [9, 162]. Conversely, nature-based interventions (NBI) such as therapeutic gardens are formally recognized as part of SUD management in Chile's 2024 Policy for Complementary Medicine and Well-being Practices [164]. Similarly, the establishment of healing gardens in rehabilitation centers and the training of professionals by the Pan-American Association for Social and Therapeutic Horticulture (APHTS) promotes horticultural therapies across LAC (Table 5) [164]. In a recent scoping review, Venner et al. [170] highlight the need for culturally adopted medicinal plant interventions based on evidence to improve treatment outcomes. For example, programs integrating cognitive behavioral therapy (CBT) with traditional healing (curanderismo) reported higher patient

engagement compared to standard protocols [170]. These culturally adapted interventions developed through community-based participatory research (CBPR) described higher patient engagement and superior efficacy in SUD outcomes compared to standard protocols [170]. These initiatives deeply reflect growing institutional recognition and acknowledgment of the sociocultural relevance of medicinal plants in LAC. The dearth of clinical trials for medicinal plants with potential SUD management potentials is still challenging and calls for further studies. Most evidence is derived from small observational studies limiting general applications [162, 163].

5 Policies and regulations on medicinal plants in therapeutic communities for SUD in LAC

5.1 Current regulatory landscape

Most Latin American and Caribbean (LAC) countries lack explicit policies governing the use of medicinal plants in therapeutic communities (TCs) for substance use disorder (SUD) management. While some nations, such as Colombia, Brazil, Cuba, and Argentina, have integrated traditional medicine into primary healthcare systems, these frameworks rarely address SUD-specific applications [171–174]. For example, Colombia's Law 1164 (2007) provides standards for complementary therapies but does not formally recognize culturally significant plants like *Banisteriopsis caapi* [173, 174]. Similarly, Brazil's National Policy of Medicinal Plants (PNPMF) emphasizes quality control but struggles with enforcement in informal markets [175]. This regulatory ambiguity creates disparities in safety protocols, dosing standardization, and integration of TC practices into formal healthcare systems.

5.2 Regional harmonization initiatives

Efforts to harmonize regulations across LAC include the Caribbean Regulatory System (CRS) and the Latin America and Caribbean Medicinal Devices Regulatory Agency (AMLAC). Established under CARPHA, CRS accelerates approvals for conventional medicines by relying on evaluations from agencies like the WHO or EMA, though its focus on herbal therapies remains limited [168]. AMLAC, launched in 2023, aims to streamline approvals for medical devices and pharmaceuticals across member states, fostering mutual recognition of regulatory decisions [169]. While AMLAC currently prioritizes synthetic drugs, its mandate for "health self-sufficiency" could eventually extend to evidence-based herbal products for SUD [169].

5.3 National efforts in pharmacovigilance and traditional medicine

Several countries have initiated pharmacovigilance systems to monitor medicinal plant safety. Brazil maintains a drug-monitoring system for dependence risk substances, which could theoretically include herbal therapies [176]. Also, Cuba's Center for State Control of Medicines (CECMED) regulates biopharmaceuticals and promotes research into plant-based therapies, aligning with its healthcare self-sufficiency goals [169]. Similarly, Argentina categorizes herbal products as dietary supplements or non-prescription medicines but lacks enforceable national laws [172]. Despite these efforts, inconsistent enforcement and limited focus on SUD-specific pathways hinder progress [174].

5.4 PAHO and international collaboration

The Pan American Health Organization (PAHO) plays a pivotal role in advancing SUD policies. Its 2021 project to improve SUD management in LAC focuses on capacity-building, training healthcare workers, and fostering collaboration between national agencies [9]. PAHO's Universal Care for Substance Use Disorders framework emphasizes prevention, treatment, and recovery but lacks explicit guidelines for plant-based therapies (9). Collaborations with international bodies like the United Nations Office on Drugs and Crime (UNODC) and the Inter-American Drug Abuse Control Commission (CICAD) further strengthen regional responses, though integration of traditional practices remains peripheral [9, 174].

5.5 Challenges and future directions

Key barriers to evidence-based integration include:

Standardization gaps: Variability in plant cultivation, preparation, and dosing complicates quality control [175, 177].

Cultural and ethical oversights: Policies often neglect ancestral knowledge and community-driven methodologies, risking misinterpretation of plant efficacy [174, 178].

Limited clinical evidence: Only 6% of Brazilian Amazonian medicinal plant studies reach clinical trial phases, prioritizing ethnobotanical documentation over translational research [175].

Regulatory reliance: While 13 LAC countries (e.g., Mexico, Peru) use FDA/EMA approvals to expedite drug registrations, this practice rarely extends to herbal products [177].

Future steps should prioritize:

Culturally informed frameworks: Engaging Indigenous communities in policy design to align regulations with traditional practices [174].

Targeted research: There is need to conduct clinical trials on SUD-specific mechanisms (e.g., GABAergic modulation by *Scutellaria lateriflora*) [175].

Regional collaboration: There is need to leverage AMLAC and CRS to develop standardized protocols for herbal product safety and efficacy [169].

While LAC has made strides in regional harmonization and national pharmacovigilance, the absence of SUD-specific policies for medicinal plants in TCs reflects a critical gap. Bridging traditional knowledge with evidence-based regulation—through PAHO-led initiatives, clinical validation, and community engagement—will be essential to harnessing the region's botanical heritage for sustainability.

6 Research gaps and future outlook on plant-based therapies for SUD in LAC

Based on the outcome of our review, presently significant research gaps hinder the evidence-based integration of plant-based therapies for managing SUD into modern healthcare systems despite their deeply rooted cultural and traditional relevance. Developing culturally informed regulatory frameworks, promoting interdisciplinary collaboration, and the need to prioritize clinical trials will address these gaps. Harmonization efforts to ensure equitable, safe, and evidence-based integration of medicinal plants into SUD care must align with the Latin American and Caribbean Medicines Regulatory Agency's (AMLAC) objectives and research goals [174, 175]. The research gaps and future outlook are summarized in Table 6.

6.1 Limited clinical trials and translational research

Presently, clinical trials on medicinal plants relevant to SUD management are limited and inadequate in LAC despite the availability of few preclinical studies on many medicinal plants, such as those that highlight the anti-inflammatory and neuroprotection mechanisms of *Z. officinale* and *T. diffusa* significant to SUD. Most studies on medicinal plants focus on in vitro models or basic chemical characterization of early Technology Readiness Levels (TRL 1–3) rather than human trials [175]. For instance, at the moment, only an estimated 6% of Brazilian Amazonian medicinal plant publications have reached phase I clinical trials (TRL 6), and the majority of the publications prioritize ethnopharmacological characterization and documentation over clinical validation [175]. This gap significantly delays the transition of traditional knowledge of medicinal plants into clinically regulated therapies for substance addiction recovery.

Table 6 Research gaps and future outlook on plant-based therapies for SUD in LAC

Research gaps	Future outlook	References
1. Limited clinical trials and translational research Preclinical studies dominate; few human trials Only ~6% of Brazilian Amazonian medicinal plant studies reach clinical validation (TRL 6)	Prioritize clinical trials and translational research to bridge traditional knowledge with regulated therapies	[175]
2. Fragmented collaboration and standardization Siloed research networks; lack of cross-institutional partnerships Variability in plant preparation, dosing, and cultivation	Strengthen international collaboration and standardize protocols for cultivation, preparation, and dosing	[174, 175]
3. Ethical and cultural considerations Neglect of ancestral knowledge in research design Limited frameworks for compensating Indigenous communities	Integrate community-driven methodologies and ethical frameworks to protect cultural heritage and ensure equitable benefit-sharing	[178]
4. Toxicity and safety profiling Inadequate safety data for many plants Weak enforcement of quality control (e.g., Brazil's PNPMF)	Develop robust toxicity frameworks and improve pharmacovigilance systems to ensure safe usage	[174, 178]
5. Multidisciplinary training and policy integration Minimal ethnopharmacology training for healthcare providers Few countries formally recognize medicinal plants in SUD policies	Integrate policies into regulatory frameworks and train healthcare workers on herb-drug interactions and dosing guidelines	[174, 177]
6. Targeted research on SUD-specific mechanisms Studies focus on general health (e.g., diabetes) rather than addiction pathways (e.g., dopamine modulation)	Prioritize research on SUD-specific mechanisms (e.g., withdrawal symptom management, neurotransmitter modulation)	[175, 178]

6.2 Fragmented collaboration and standardization challenges

Limited international or cross-institutional partnerships exist for LAC research networks, often siloed. For instance, recent bibliometric analyses reveal that the country that dominates medicinal plant research in LAC is Brazilian via its institutions. However, lack of cohesive collaboration with global clinical trial hubs like the EU or USA has significantly limited translational research opportunities for Brazil and the region [174, 175]. In addition, plant variabilities in species and cultivation, methods of herbal preparations, and dosing add to the complexities of medicinal plants standardization in the region. Recent reports indicated that inconsistencies in efficacy claims of over 500 medicinal plants used for health by the Caribbean and Latin diaspora communities in New York noted less than 5% of the plants studied systematically [178]. These standardization and collaboration gaps need to be urgently addressed to facilitate improved utilization of medicinal plants in LAC.

6.3 Ethical and cultural considerations in research design

At the moment, despite their deep ties to Afro-descendants and indigenous traditions, research often neglects the cultural competence of medicinal plant therapies, side-lining ancestral knowledge or risking misinterpretation of plant efficacies. A few studies of diaspora Caribbean accentuated that an estimated 90% of study participants trust medicinal plant therapies compared to conventional medications [178]. However, research

clinical protocols seldom integrate community-driven methodologies or traditional healers, in the process, relegating ancestral knowledge [175, 178]. In addition, compensation for traditional knowledge and Indigenous communities is limited and underdeveloped due to lack of ethical frameworks to address such challenges [178]. Establishing proper cultural and ethical considerations in medicinal plant research, especially for SUD, will increase the incorporation of traditional ancestral knowledge and the interpretation of plant efficacy.

6.4 Toxicity and safety profiling of medicinal plants

Despite widespread utilization, safety and toxicological data on many medicinal plants are currently inadequate or lacking. For instance, many Puerto Rican communities use *P. incarnate* for anxiety relief in SUD populations. However, the risk of hepatotoxicity from improper preparation or adulterants is poorly documented [174, 178]. Similarly, even though in Brazil, emphasis on quality control is made by the National Policy of Medicinal Plants (PNPMF), enforcement is inconsistent and weak, particularly in informal markets or rural settlements [175]. There is a need for LAC member states to prioritize toxicity and safety framework for medicinal plants in LAC, especially for SUD management (Table 6).

6.5 Multidisciplinary training and policy integration

At present, very few countries such as Brazil and Cuba have integrated traditional medicine into public healthcare systems; most countries in Latin America and the Caribbean lack formal policies for medicinal plants, particularly therapies for SUD management [174]. For instance, despite its cultural significance and potential for SUD management, *B. caapi* lacks legal recognition in Colombia due to a clash between traditional practices and regulatory frameworks [174]. Integrating policies for traditional medicinal plants into regulatory frameworks may improve the management of SUD, particularly with plant-based therapies (Table 6). In addition, the need to train healthcare providers with adequate knowledge of medicinal plants cannot be overemphasized. Presently, minimal training in ethnopharmacology is provided to healthcare personnel, limiting patient–provider collaboration on dosing guidelines and herb–drug interactions [174, 178].

6.6 Targeted research on SUD-specific mechanisms

Targeted medicinal plant research, particularly on substance use disorders in LAC, is very limited or does not exist as most ethnopharmacological studies focus on general health, such as diabetes, inflammation, hypertension, and other diseases, rather than SUD-specific pathways like withdrawal symptom management or dopamine modulation [175]. For example, presently a few studies reported the GABAergic effects of *S. lateriflora* (skullcap); however, the plant's direct application to alcohol or opioid dependence remains largely unexplored [175, 178]. Targeting medicinal plant studies on substance use disorder-specific mechanisms in LAC will provide evidence-based alternative therapies that will guide policy formations in the region (Table 6).

6.7 Limitations

This review attempted to identify and present rudimentary literature on medicinal plants with potential for SUD treatment. The review, however, has some notable limitations. For instance, the review needed to provide adequate nuanced consideration in the discussion surrounding the mechanism of action of these plants proposed for use in managing SUD, but limited published research narrowed this effort. Also, understanding how the plants' mechanisms of action link to LAC communities' cultural and behavioral backgrounds and interact with additional pathways would have been vital to understanding how the native plants may be leveraged in patients with SUD but due to lack of robust clinical evidence this pose a limitation to the review. Additionally, a large proportion of the evidence base is derived from animal studies; we admit that a more in-depth discussion

surrounding the applicability and generalizability of these preliminary studies would have been provided despite the review being a baseline narrative. In addition, a dearth of information exists in articles published specifically highlighting the use of traditional medicines for substance use disorders in the Caribbean and Latin America. A systematic review would have brought a better synthesis of existing literature; however, more published articles are needed to provide robust statistical power for such an effort. Presently, such published articles needed for a systematic review are inadequate. The absence of quality assessment frameworks for traditional medicinal plants studies risks including low-quality or biased data; hence, the narrative review methodological approach presented here. Furthermore, the review did not offer complex plant bioactive structures and molecular pathways but identified and presented rudimentary literature for SUD, presenting another limitation. To the best of our knowledge, this is one of the few attempts to identify and present a review on medicinal plants used to treat SUD in Latin America and the Caribbean and hence the study's strength.

7 Conclusion

The exploration of 12 medicinal plants native to Latin America and the Caribbean (LAC) reveals a rich tapestry of bioactive compounds and cultural practices that hold promise for addressing substance use disorders (SUDs). Among these, β -carbolines (e.g., harmine in *Banisteriopsis caapi*), flavonoids (e.g., apigenin in *Matricaria recutita*), and kavalactones (e.g., kavain in *Piper methysticum*) emerge as key players, modulating critical neurochemical pathways such as GABAergic signaling, monoaminergic balance, and neuroinflammatory responses. These compounds not only align with preclinical evidence—such as harmine's 40% reduction in alcohol self-administration in rodents, but also resonate with centuries-old traditions. For instance, Amazonian ayahuasca rituals (*B. caapi*), Caribbean herbal blends for anxiety (*Leonotis nepetifolia*), and Andean adaptogenic therapies (*Lepidium meyenii*) exemplify how cultural wisdom and biodiversity converge to offer holistic solutions for addiction.

However, the translation of these traditional practices into mainstream healthcare requires urgent clinical validation and policy support. While plants like *Hypericum perforatum* demonstrate multi-target efficacy (e.g., hyperforin's TRPC6 modulation), their integration is hindered by herb–drug interaction risks and inconsistent regulatory frameworks. Despite these barriers, these medicinal plants present affordable, accessible, and culturally relevant options for the management of SUD in resource-limited setting peculiar to LAC. To bridge this gap, collaborative efforts must prioritize standardized

clinical trials to conduct rigorous studies mirroring traditional preparation methods (e.g., aqueous extracts) to validate efficacy and safety. In addition, community-led research engaging indigenous healers and local communities to preserve ethnopharmacological knowledge while ensuring equitable benefit-sharing. Finally, policy harmonization to develop region-specific guidelines under initiatives like AMLAC to regulate quality control and mitigate adulteration risks should be prioritized. By uniting ancestral knowledge with modern science, LAC can pioneer a culturally grounded, evidence-based paradigm for SUD treatment—one that honors its ecological and cultural heritage while addressing the urgent global burden of addiction.

Abbreviations

AMLAC	Latin America and Caribbean medicinal devices regulatory agency
AMPA	A-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
APHTS	Pan-American Association for Social and Therapeutic Horticulture
BZD	Benzodiazepines
CARPHA	Caribbean Public Health Agency
CBPR	Community-based participatory research
CBT	Cognitive behavioral therapy
CECMED	Cuba's Center for State Control of Medicines
CICAD	Inter-American Drug Abuse Control Commission
CRS	Caribbean Regulatory System
DMT	Dimethyltryptamine
EMA	European Medicines Agency
EU	European Union
FST	Forced swim test
GABA	Gama amino butyric acid
GAD67	Glutamate decarboxylase 67
HPA	Hypothalamic–pituitary–adrenal
HT	Hydroxytryptamine
JNK	Jun N-terminal kinases
LAC	Latin America and the Caribbean
LILACS	Latin American and Caribbean Health Sciences Literature
MAO	Monoamine oxidases
MDA	Malondialdehyde
NADPH	Nicotinamide adenine dinucleotide phosphate hydrogen
NBI	Nature-based interventions
NIDDKD	National Institute of Diabetes and Digestive and Kidney Diseases
NMDA	N-Methyl-D-aspartate receptor
OAS	Organization of American States
Ox-LDL	Oxidized low-density lipoprotein
PAHO	Pan American Health Organization
PNPMF	National Policy of Medicinal Plants
RIOD	Ibero-American network of non-governmental organizations working on drug dependence
SUD	Substance use disorders
TC	Therapeutic communities
THH	Tetrahydroharmine
TNF	Tumor necrosis factor
TRAMIL	Traditional Medicines in the Islands (program of allied research to popular medicines in the Caribbean)
TST	Tail suspension test
UNODC	United Nations Office on Drugs and Crime
US	United States
WHO	World Health Organization

Author contribution

DCH and OEO contributed to conception, supervision, and literature search and reviewed and edited the final draft. IEN, JHC, and GMS performed literature search and writing and reviewed and edited the final draft. All the authors read and approved the final manuscript.

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Data availability

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Declarations

Conflict of interest

The authors declare no competing interests.

Ethical approval and consent to participate

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