Plant Medicines in Indigenous Mental Health Care: Traditional Knowledge, Contemporary Evidence, Ethical Principles, and Pathways for Respectful Integration

Daniel Charles Crosser
daniel@lonestarhealing.org

May 9, 2026

Abstract

Indigenous plant medicines—such as ayahuasca (*Banisteriopsis caapi* + *Psychotria viridis*), peyote (*Lophophora williamsii*), and iboga (*Tabernanthe iboga*)—have been used for millennia in ceremonial contexts to support mental, emotional, spiritual, and communal well-being. These "teacher plants" or sacred relatives form the foundation of holistic Indigenous health paradigms that view mental distress as an imbalance within relationships to self, community, ancestors, and the natural world. Western psychedelic research has seen a resurgence of interest in these substances for conditions including depression, anxiety, post-traumatic stress disorder (PTSD), substance use disorders (SUDs), and traumatic brain injury (TBI). However, this interest has often occurred without Indigenous leadership, raising concerns of cultural appropriation, epistemic injustice, unsustainable harvesting, and exclusion from benefit-sharing.

This review synthesizes historical-cultural contexts, scientific evidence from ritual and clinical studies, neurobiological and relational mechanisms, and Indigenous-led ethical frameworks. Key findings include sustained reductions in depressive and anxious symptoms following ayahuasca use in ritual settings, marked improvements in PTSD, depression, and functioning from ibogaine-assisted treatment in veterans with TBI, and no detectable psychological or cognitive deficits among long-term ceremonial peyote users in the Native American Church. Ethical principles from an Indigenous global consensus—Reverence, Respect, Responsibility, Relevance, Regulation, Reparation, Restoration, and Reconciliation—provide a roadmap for decolonizing psychedelic science.

We highlight promising Indigenous-led models (e.g., the Yaqui Intercultural Medicine Clinic) and advocate for Two-Eyed Seeing (Etuaptmumk) approaches that integrate Indigenous and Western knowledge systems equitably. Future directions prioritize Indigenous sovereignty, community-based protocols, and reciprocal partnerships to ensure plant medicines continue serving mental health in culturally congruent ways.

Keywords: ayahuasca; peyote; iboga; ibogaine; Indigenous mental health; decolonial science; Two-Eyed Seeing; psychedelic ethics; traditional medicine; cultural sovereignty.

1 Introduction

Mental health disorders constitute one of the most significant public health challenges of our time. The World Health Organization estimates that more than one billion people worldwide live with a mental health condition [30], with depression and anxiety alone generating an annual global economic burden exceeding $1 trillion in lost productivity. These figures, however, mask profound inequities. Indigenous populations across the Americas, Australia, and beyond experience disproportionately high rates of depression, anxiety, PTSD, SUDs, and suicide. In the

United States, non-Hispanic Indigenous people die by suicide at higher rates than any other racial or ethnic group; among Native American youth, suicide is the second leading cause of death, with rates more than double those of White youth. In Canada, First Nations suicide rates are three times the national average, Métis rates are twice as high, and Inuit rates reach nine times the non-Indigenous baseline, reaching the world's highest recorded rates in some Nunavut communities. These disparities are not merely biomedical; they are rooted in historical and ongoing colonial trauma, land dispossession, cultural suppression, and systemic racism—factors that Western psychiatric models often fail to address adequately.

Indigenous conceptions of mental health stand in stark contrast to dominant Western biomedical frameworks. Where Western psychiatry frequently pathologizes symptoms as discrete biochemical imbalances located within the individual brain (treatable primarily through pharmacotherapy or cognitive-behavioral interventions), Indigenous knowledge systems view mental wellness as relational, holistic, and embedded within a web of interconnections. Health encompasses harmony among mind, body, spirit, community, ancestors, and the natural world (often conceptualized as "land" or "Country"). Illness, including mental distress, is understood as an imbalance or disconnection arising from disrupted relationships rather than an isolated pathology. As Gone [9] has articulated through decades of collaborative work with tribal communities, Indigenous frameworks reframe "mental health problems" as postcolonial disorders, calling for an "alter-Native psy-ence" that centers culture, history, spirituality, and collective healing over neoliberal individualism.

Within these holistic paradigms, plant medicines—often referred to as "teacher plants," "sacred relatives," or "spirit medicines"—have served as central therapeutic and diagnostic tools for millennia. Amazonian traditions employ ayahuasca (*Banisteriopsis caapi* + *Psychotria viridis*) in ceremonial contexts for spiritual diagnosis, emotional processing, and communal restoration among Shipibo, Asháninka, and other nations. North American Indigenous practices integrate peyote (*Lophophora williamsii*) within the Native American Church and Huichol ceremonies to foster balance and recovery from addiction. Central African Bwiti traditions use iboga (*Tabernanthe iboga*) for initiation, trauma resolution, and addiction interruption. Across these diverse cultures, the plants are not mere pharmacological agents but sentient kin that facilitate reconnection, insight, and relational repair when used within rigorous ceremonial protocols emphasizing intention (set), sacred space (setting), community integration, and ecological reciprocity [2].

The contemporary "psychedelic renaissance"—marked by renewed clinical interest in compounds such as psilocybin, MDMA, ayahuasca, and ibogaine for treatment-resistant depression, PTSD, end-of-life anxiety, and SUDs—has brought unprecedented visibility to these substances. Yet this resurgence has largely occurred within Western scientific and therapeutic frameworks that frequently detach the medicines from their Indigenous origins. While early clinical trials demonstrate promising efficacy (e.g., rapid and sustained symptom reduction in controlled settings), the movement has drawn sharp critique for perpetuating patterns of cultural appropriation, epistemic injustice, and extractivism [24]. Indigenous Nations and scholars have highlighted the exclusion of traditional knowledge holders from research design, funding, and benefit-sharing; the commodification of sacred plants through retreat tourism and patenting; unsustainable harvesting driven by global demand; and the risk that decontextualized, medicalized use may erode the very relational and spiritual dimensions that underpin therapeutic success in traditional settings.

In response to these concerns, Indigenous-led initiatives have articulated clear ethical guardrails. A globally representative Indigenous consensus process [5] identified eight interconnected principles—Reverence, Respect, Responsibility, Relevance, Regulation, Reparation, Restoration, and Reconciliation—to guide any Western engagement with traditional Indigenous medicines. These principles emphasize kincentric worldviews, free prior and informed consent (FPIC), Indigenous leadership and governance, environmental stewardship, restitution for historical harms, and genuine reciprocity rather than extraction. Complementary frameworks

such as Mi'kmaq Etuaptmumk (Two-Eyed Seeing[1]) offer practical pathways for equitable integration: learning to see with one eye through the strengths of Indigenous knowledges and ways of knowing, and with the other through Western science, using both together for the benefit of all [1].

This paper reviews the historical-cultural contexts, contemporary scientific evidence, mechanisms of action, and promising community-led models of plant medicines in Indigenous mental health care. It does so while foregrounding the ethical imperatives derived from Indigenous consensus and lived experience. By synthesizing observational, longitudinal, and emerging clinical data alongside traditional knowledge systems, we aim to illuminate both the therapeutic potential of these medicines and the non-negotiable requirements for respectful, decolonial engagement. The following sections examine cultural foundations (Section 2), efficacy evidence (Section 3), mechanisms (Section 4), ethical-legal challenges (Section 5), exemplary integration models (Section 6), future directions (Section 7), and concluding reflections (Section 8). In doing so, we seek to contribute to a growing movement that honors Indigenous sovereignty, protects sacred knowledge, and advances mental health pathways that are culturally congruent, relationally grounded, and ecologically sustainable.

2 Historical and Cultural Contexts

Plant medicines occupy a sacred, relational position within Indigenous knowledge systems worldwide. Far from being viewed as mere pharmacological agents or isolated psychoactive compounds, they are understood as "teacher plants," "sacred relatives," or living intelligences—sentient kin with whom humans enter into reciprocal relationships of respect, reciprocity, and stewardship. This kincentric ontology frames mental health not as an individual biochemical imbalance but as a disruption in the web of relationships connecting self, community, ancestors, land, and the spirit world. Healing therefore requires restoring balance through ceremony, intention, and communal integration rather than symptom suppression alone.

Across continents and millennia, specific plant medicines have been stewarded by Indigenous Nations as central tools for diagnosis, emotional processing, spiritual insight, and communal restoration. The three most prominent examples—ayahuasca in Amazonian traditions, peyote in North and Central American practices, and iboga in Central African Bwiti—illustrate both the diversity and the shared principles of Indigenous plant medicine. Each is embedded in rigorous ceremonial protocols that emphasize preparation (dietary and spiritual), guided experience, integration, and ecological reciprocity. These practices predate European contact by centuries to millennia and have persisted despite colonial suppression, offering profound models for addressing what Western frameworks term "mental health" challenges such as trauma, addiction, depression, and existential disconnection.

2.1 Amazonian Traditions: Ayahuasca among the Shipibo-Conibo and Asháninka

In the Upper Amazon basin, ayahuasca (prepared from the *Banisteriopsis caapi* vine and the DMT-containing leaves of *Psychotria viridis*) has been used for centuries by numerous Indigenous groups, with some scholars proposing far older origins on the basis of oral history and partial archaeological evidence [23]. Among the Shipibo-Conibo people of Peru's Ucayali River region,

[1] **Glossary of non-English terms used in this review.** *Icaros*: sacred songs sung by Amazonian healers to channel plant spirits during ceremony. *Temazcal*: Mesoamerican sweat-lodge ceremony. *Eboka*: Bwiti term for life force or vital essence (also used as a name for iboga). *Nganga*: Bwiti healer/initiator. *Mbandja*: Bwiti village temple. *Wirikuta*: sacred Wixárika pilgrimage site in San Luis Potosí, Mexico. *Etuaptmumk*: Mi'kmaw word for Two-Eyed Seeing, the practice of integrating Indigenous and Western knowledges. *Rao Nete*: Shipibo-Conibo concept of the world of plant spirits. *Oni / nishi-pai*: Shipibo-Conibo names for the ayahuasca brew. *Onaya*: Shipibo-Conibo healer. *Sabedoras*: Indigenous Amazonian women knowledge keepers ("those who know"). *Curanderismo*: traditional healing system common across Latin America.

ayahuasca (known locally as *oni* or *nishi-pai*) is a cornerstone of *curanderismo*, a sophisticated healing system. Shipibo healers (often called *onaya* or shamans) traditionally consume the brew themselves during ceremonies to enter the *Rao Nete* (world of plant spirits), diagnose the energetic, emotional, or spiritual roots of illness, and channel healing through *icaros*: sacred songs that invoke plant spirits. Patients receive treatment via these songs, plant prescriptions, and direct energetic work rather than ingesting the brew themselves in many classical contexts.

The Asháninka (or Ashaninka) people, whose territories span Peru and Brazil, similarly integrate ayahuasca into communal and individual healing. Ceremonies serve spiritual diagnosis, trauma resolution, and the restoration of harmony within families and communities. Ayahuasca is revered as a "vine of the spirits" or "vine of the dead," acting as a portal that reveals hidden causes of suffering, often understood as sorcery, ancestral imbalance, or disconnection from the forest. Oral traditions describe the plant as a gift from the spirits themselves, discovered through direct communication with the jungle. Healing is inherently relational: ceremonies strengthen community bonds, reinforce moral teachings, and foster ecological stewardship, as seen in Asháninka efforts to protect Amazonian territories through spiritual mandates rooted in ayahuasca visions.

In both traditions, mental distress is addressed holistically. Visions and insights facilitated by the brew enable emotional catharsis, insight into personal and collective traumas, and reconnection with ancestral knowledge. The ceremonial "set and setting"—including strict dietary taboos (e.g., avoidance of salt, sugar, and sexual activity), *icaros*, tobacco smoke, and post-ceremony integration—ensure safety and depth. These protocols underscore that the plant's efficacy is inseparable from its cultural container [27].

2.2 North and Central American Traditions: Peyote in Huichol/Wixárika and Native American Church Practices

Peyote (*Lophophora williamsii*), a small spineless cactus native to the Chihuahuan Desert, has been used ceremonially for at least 5,700 years, with carbon-dated specimens from Texas caves confirming pre-Columbian ritual use dating to 3780–3660 BCE [4]. Among the Wixárika (Huichol) people of Mexico's Sierra Madre Occidental, peyote remains central to an unbroken tradition of pilgrimage and ceremony. Wixárika practitioners describe peyote as "everything": a crossing of souls that facilitates direct communion with deities, ancestors, and the natural world. Annual pilgrimages to sacred sites (such as *Wirikuta*) involve consuming peyote to receive visions that guide personal healing, community decision-making, and resistance to external threats. These experiences foster "communitas" [28], novel problem-solving, resilience, and a deepened sense of interconnectedness that supports cultural survival amid ongoing land disputes.

In the United States and Canada, peyote's sacramental use expanded northward in the late 19th century through visionary leaders among the Kiowa, Comanche, and other Plains tribes. This gave rise to the Native American Church (NAC), formally incorporated in 1918 as a pan-Indian religious movement that blends Indigenous spiritual elements with select Christian teachings. NAC ceremonies are typically all-night gatherings held in a tipi or dedicated space, involving the ritual consumption of peyote buttons or tea, prayer, drumming, and songs. Participants seek guidance from the "Peyote Spirit" (sometimes identified with or alongside Jesus as an intercessor), addressing mental health challenges such as addiction, grief, and intergenerational trauma. The medicine is understood to promote introspection, moral clarity, and spiritual power, with documented benefits for recovery from alcohol and substance use disorders.

U.S. federal law (American Indian Religious Freedom Act Amendments of 1978 and subsequent rulings) protects NAC members' religious use of peyote, recognizing its role in cultural continuity and well-being. As with ayahuasca, the ceremonial context—preparation, communal witnessing, and post-ceremony reflection—is essential; isolated use outside these frameworks is viewed as incomplete or disrespectful.

2.3 Central African Traditions: Iboga in Bwiti

In Gabon and neighboring regions of Central Africa, the root bark of *Tabernanthe iboga* is the cornerstone of Bwiti, a vibrant spiritual tradition practiced primarily by the Fang, Mitsogo, Punu, and Apindji peoples (with origins traced to ancient Pygmy/Bobongo forest knowledge). Iboga (regarded as both "father and mother" and the highest intelligence among plants) has been used for centuries in initiation rites, healing ceremonies, and community governance. Bwiti ceremonies, often held in village temples (*mbandja*), involve large doses of iboga root for profound visionary journeys that connect participants with ancestors, reveal hidden truths, and facilitate personal and collective transformation.

Initiation with iboga is a rite of passage that confronts mortality, resolves spiritual blockages, and restores life force (*eboka*). It addresses what might be termed mental or emotional distress through direct ancestral dialogue, emotional release, and bloodline healing. Bwiti leaders emphasize iboga's role in stabilizing families, resolving conflicts, and maintaining ecological and social harmony. As in Amazonian and North American traditions, the medicine is never isolated from ritual: participants undergo extensive preparation, are guided by experienced *nganga* (healers), and integrate experiences through song, dance, and community support.

2.4 Shared Ontologies and Ceremonial Principles

Despite geographic separation, these traditions share core features: plants are active agents in a living cosmos; healing is relational and multi-generational; and ceremony provides the essential container for safe, meaningful engagement. Dietary restrictions, sacred songs or music, communal witnessing, and post-experience integration are universal safeguards that amplify therapeutic outcomes while minimizing risk. Mental health benefits—reduced depression, anxiety, addiction, and PTSD symptoms—emerge not primarily from the molecule but from restored relationships with self, community, ancestors, and land.

2.5 Colonial Impacts and Cultural Resilience

European colonization brought suppression of these practices—through missionary prohibitions, criminalization, and cultural erasure—yet Indigenous Nations maintained them underground or reframed them within syncretic movements such as the NAC. Today, these medicines embody resilience and decolonial assertion. Their continued vitality demonstrates that Indigenous mental health frameworks predate biomedical models by millennia and address dimensions of postcolonial distress that biomedical approaches often overlook.

In summary, the historical and cultural contexts of ayahuasca, peyote, and iboga reveal plant medicines as sophisticated, time-tested technologies for relational healing. Any contemporary integration must therefore honor these living traditions rather than extract their active compounds.

3 Scientific Evidence on Efficacy

Approach. This review is presented as a narrative synthesis rather than a PRISMA-style systematic review. We draw on peer-reviewed clinical trials, prospective and longitudinal naturalistic studies, ethnographic fieldwork, and Indigenous-led community evaluations published primarily between 2005 and 2025. Priority is given to studies that preserve or document the ceremonial context of use, and to Indigenous-governed research where available. Where evidence is sparse or methodologically limited, this is stated explicitly.

Evidence on Indigenous plant medicines is predominantly observational and naturalistic, reflecting the medicines' embedding in cultural and ritual contexts rather than isolated pharmacological administration. The body of work is limited by small-to-moderate sample sizes,

lack of randomization, self-selection bias, and short follow-up periods (typically 1–12 months). Indigenous-led and community-based programs provide particularly valuable insights, as they preserve the relational and ceremonial frameworks that appear essential to sustained outcomes.

3.1 Ayahuasca in Amazonian and Intercultural Ritual Contexts

Ayahuasca has received the most empirical attention among the three focal medicines. Early open-label and longitudinal studies among first-time (naïve) users demonstrated rapid and sustained symptom relief. In a combined longitudinal and cross-sectional investigation of 40 ayahuasca-naïve participants (many presenting with baseline psychiatric symptoms), Jiménez-Garrido et al. [13] reported clinically meaningful reductions in depression (measured by the Hamilton Depression Rating Scale) and overall psychopathology at 1-month and 6-month follow-ups, with effect sizes reaching moderate-to-large levels (Cohen's $d \approx 0.72$ at 6 months). Long-term regular users ($n = 23$) exhibited significantly lower depression scores, higher self-transcendence, and improved quality of life compared with naïve users, suggesting cumulative benefits tied to repeated ceremonial engagement. An earlier open-label study by Osório et al. [17] likewise reported rapid antidepressant effects after a single dose of ayahuasca in patients with recurrent depression.

Larger naturalistic surveys reinforce these findings. Perkins et al. [19] followed 53 participants before and after facilitated ayahuasca ceremonies; one month post-ceremony, significant reductions emerged in depression, anxiety, stress, alcohol and cannabis use, negative affect, and impulsivity, alongside increases in positive mood, self-efficacy, extraversion, agreeableness, spirituality, and relationship satisfaction. Baseline traits such as high negative emotionality and low self-efficacy strongly predicted greater improvements, highlighting individual responsiveness within ritual settings. A complementary international cross-sectional survey of 11,912 ayahuasca consumers reported parallel patterns of self-reported reductions in depression and anxiety [25], while ritual-context studies have linked ayahuasca specifically with reductions in addiction severity and shifts in self-narrative [7, 27]. A six-month prospective study at an Amazonian retreat further documented sustained reductions in depression, anxiety, and global distress, with concomitant increases in self-compassion [22].

More recent prospective and community-based data further strengthen the evidence base. Pagni et al. [18] documented persisting improvements in mental health and well-being up to 12 months following naturalistic ayahuasca use, with the largest symptom reductions observed among those diagnosed with depressive or anxiety disorders. Lowe et al. [15] similarly reported long-term reductions in depression, anxiety, and shame in a cohort of Middle Eastern and North African immigrants and refugees following ceremonial use. A 2024 systematic review by Sheth et al. [26] synthesized 43 studies (published September 2017–May 2023) and concluded that ayahuasca shows consistent therapeutic potential across depression, anxiety, SUDs, eating disorders, and PTSD, particularly when the ritual container—shamanic guidance, *icaros* (sacred songs), dietary preparation, and communal integration—is preserved.

Indigenous-led programs provide some of the most culturally congruent evidence. In the Yaqui Intercultural Medicine Clinic in Sonora, Mexico (an outpatient program founded and operated by Yaqui health professionals and traditional healers), preliminary observational data from 37 participants [8] showed dramatic reductions after just one or two ayahuasca ceremonies. Mean Beck Depression Inventory-II scores dropped from 15.7 to 5.1; Beck Anxiety Inventory scores fell from 16.6 to 6.3; and Inventory of Complicated Grief scores decreased from 39.6 to 10.7. Among eight individuals presenting with suicide risk, seven cases resolved after a single ceremony. These changes were sustained through follow-up assessments, with no serious adverse events reported. The program explicitly integrates ayahuasca within Yaqui cultural protocols, *temazcal* sweat-lodge ceremonies, and community support, underscoring the therapeutic synergy of Indigenous frameworks.

3.2 Peyote in Native American Church and Wixárika Practices

Empirical data on peyote are more limited but consistently positive regarding long-term safety and mental health correlates. The landmark study by Halpern et al. [10] compared 61 Navajo members of the Native American Church (regular peyote users) with 36 former alcohol-dependent individuals and 79 minimal-substance-use controls. Using the Rand Mental Health Inventory and a battery of ten neuropsychological tests, the authors found no detectable psychological or cognitive deficits among long-term peyote users; in fact, the NAC group scored significantly better than controls on several mental health indices. Lifetime peyote consumption showed no negative association with performance, and former alcoholics (non-peyote users) exhibited clear deficits. These findings have been cited for two decades as evidence that ceremonial peyote use within the NAC is not associated with detectable residual harm in this population, and may support recovery from addiction and intergenerational trauma.

Ethnographic and observational work among Wixárika (Huichol) pilgrims and NAC participants further links peyote ceremonies to enhanced community cohesion, resilience, and reduced substance misuse. While large-scale randomized controlled trials (RCTs) remain absent (largely due to legal and cultural protections around sacramental use), the absence of detectable harm and the presence of protective associations in well-controlled comparative studies stand in contrast to recreational hallucinogen use and support peyote's role in holistic mental health maintenance.

3.3 Iboga/Ibogaine in Bwiti-Informed and Clinical Settings

Iboga and its primary alkaloid ibogaine have shown particularly striking results in trauma-related conditions, especially among veterans. The Magnesium–Ibogaine: Stanford Traumatic Injury to the CNS (MISTIC) protocol study [6] followed 30 male special operations veterans with mild-to-moderate TBI and repeated blast exposures. Participants received a single dose of ibogaine (≈ 12 mg/kg) with intravenous magnesium for cardiac protection, alongside preparatory and integrative support. One month post-treatment, PTSD symptoms (Clinician-Administered PTSD Scale for DSM-5) decreased by an average 88% (Cohen's $d = 2.54$), depression (Montgomery–Åsberg Depression Rating Scale) by 87% ($d = 2.80$), and anxiety (Hamilton Anxiety Rating Scale) by 81% ($d = 2.13$). Functional disability scores dropped from moderate (30.2) to none (5.1) on the World Health Organization Disability Assessment Schedule. Cognitive improvements in concentration, memory, and impulsivity were also observed, with no serious adverse events. A follow-up analysis by Brown et al. [3] linked the intensity of mystical-type experiences during the session—measured with the Mystical Experiences Questionnaire (MEQ30)—to greater PTSD reductions both immediately and at one month, and to electroencephalographic shifts in peak alpha frequency.

These outcomes align with Bwiti traditional use, where iboga facilitates deep ancestral and emotional processing in ceremonial contexts. While the MISTIC study was open-label and conducted outside formal Bwiti settings, it incorporated elements of preparation, monitoring, and integration—features that echo Indigenous protocols and likely contributed to efficacy and safety.

3.4 Synthesis, Limitations, and Implications for Future Research

Across ayahuasca, peyote, and iboga/ibogaine, common patterns emerge: (1) rapid onset of symptom relief, often within days; (2) durability of benefits when embedded in supportive ritual and community integration; (3) improvements spanning multiple symptom domains (mood, anxiety, trauma, addiction); and (4) apparent safety in screened, culturally grounded settings. Effect sizes in observational studies are often substantial (Cohen's d values in the moderate-to-large range), though direct head-to-head comparisons with standard pharmacotherapies are not yet available [11, 29].

Nevertheless, limitations are notable. Most data derive from self-report, lack active controls or blinding, and reflect self-selected participants motivated by spiritual or therapeutic intent. Cultural and contextual factors—set, setting, preparation, and post-ceremony integration—are rarely isolated, making it difficult to disentangle pharmacological from relational mechanisms. Indigenous-led research remains underrepresented in high-impact journals, and sustainability concerns (e.g., overharvesting) are seldom addressed alongside efficacy data.

These findings strongly support the therapeutic potential of plant medicines when used within or alongside their original cultural containers. They also highlight the urgent need for Indigenous-governed, community-defined outcome measures and larger, culturally attuned RCTs.

Table 1: Comparative summary of the three focal Indigenous plant medicines.

	Ayahuasca	**Peyote**	**Iboga / Ibogaine**
Plant / active compounds	*Banisteriopsis caapi* (harmine, harmaline) + *Psychotria viridis* (DMT)	*Lophophora williamsii* (mescaline)	*Tabernanthe iboga* root bark (ibogaine, noribogaine)
Primary receptor targets	5-HT$_{2A}$ partial agonism; reversible MAO-A inhibition	5-HT$_{2A}$ partial agonism (phenethylamine)	NMDA antagonism; κ-opioid agonism; σ-1 ligand; nicotinic and dopaminergic modulation
Primary ceremonial container	Amazonian *curanderismo* (Shipibo-Conibo, Asháninka, others); *icaros*, dietary preparation, retreat-based ritual	Wixárika pilgrimage (Mexico); Native American Church all-night ceremony	Bwiti initiation and healing rites in *mbandja* temples (Gabon, Central Africa)
Headline clinical study	Yaqui Intercultural Medicine Clinic, $n = 37$ [8]	Long-term Navajo NAC users vs. controls, $n = 176$ [10]	MISTIC protocol in special-operations veterans with TBI, $n = 30$ [6]
Headline effect size	BDI-II 15.7 $\rightarrow$ 5.1; BAI 16.6 $\rightarrow$ 6.3; ICG 39.6 $\rightarrow$ 10.7; 7/8 suicide-risk cases resolved after a single ceremony	No detectable psychological or cognitive deficits; NAC users scored higher than controls on multiple mental health indices	PTSD $d = 2.54$; depression $d = 2.80$; anxiety $d = 2.13$; WHODAS 30.2 $\rightarrow$ 5.1 at one month

4 Mechanisms of Action

The therapeutic effects of these medicines emerge from three interdependent domains: neurobiological, psychological-spiritual, and cultural-relational.

4.1 Neurobiological Mechanisms

Classic serotonergic psychedelics in ayahuasca (N,N-dimethyltryptamine, DMT) and peyote (mescaline) primarily act as partial agonists at serotonin 5-HT$_{2A}$ receptors, with additional activity at 5-HT$_{1A}$, 5-HT$_{2C}$, and other subtypes. In ayahuasca, β-carboline harmala alkaloids (harmine, harmaline) inhibit monoamine oxidase-A (MAO-A), rendering DMT orally active

and prolonging serotonergic signaling. This dual action elevates serotonin availability, upregulates brain-derived neurotrophic factor (BDNF), and promotes glutamatergic neurotransmission, leading to enhanced synaptic plasticity, dendritic spine growth, and neurogenesis, particularly in prefrontal and hippocampal regions implicated in mood regulation [11, 29].

Neuroimaging studies consistently show that ayahuasca modulates large-scale brain networks. Acute administration decreases functional connectivity within the default mode network (DMN), a hub of self-referential rumination, while increasing connectivity in the salience network and executive control networks. These shifts correlate with reduced depressive rumination and enhanced cognitive flexibility, with effects persisting into the "afterglow" period (up to several weeks). Additional anti-inflammatory effects, including lowered C-reactive protein, and normalization of hypothalamic-pituitary-adrenal (HPA) axis activity further support antidepressant outcomes.

Peyote's primary alkaloid, mescaline, operates via a similar 5-HT_{2A}-mediated profile as other classic psychedelics, though its phenethylamine structure produces somewhat distinct interoceptive and emotional qualities. Long-term ceremonial use shows no neurocognitive deficits and may confer protective effects [10], consistent with 5-HT_{2A}-driven neuroplasticity without the toxicity associated with recreational use.

Ibogaine and its active metabolite noribogaine exhibit a broader, multi-target profile distinct from classic serotonergics. Ibogaine acts as an NMDA receptor antagonist, κ-opioid receptor agonist, and σ-1 receptor ligand, while also modulating nicotinic acetylcholine and dopamine systems. These actions rapidly interrupt withdrawal syndromes, promote glial cell line-derived neurotrophic factor (GDNF) release, and drive structural neuroplasticity. In the MISTIC protocol [6], a single dose produced widespread reorganization of brain networks, increased cortical thickness in multiple regions, and reduced "brain age" metrics one month post-treatment. Functional connectivity shifts (particularly posterior increases and frontal decreases) correlated directly with reductions in PTSD symptoms; the follow-up analysis by Brown et al. [3] further linked mystical-experience intensity to high-beta-network reorganization and to reductions in peak alpha frequency, suggesting targeted modulation of stress-response circuits.

Common across all three medicines is the promotion of neuroplasticity and entropy (increased brain signal diversity), which may "reset" rigid maladaptive patterns in depression, PTSD, and addiction. Preclinical rodent models confirm BDNF–TrkB signaling in the infralimbic cortex as a critical mediator of fear extinction and fear generalization reduction following ayahuasca-like treatments.

4.2 Psychological and Spiritual Mechanisms

Beyond molecular pathways, plant medicines induce acute altered states characterized by mystical-type experiences, emotional catharsis, and profound insight. Validated scales such as the Mystical Experience Questionnaire (MEQ) show that higher scores during sessions predict greater long-term reductions in depression, anxiety, and PTSD symptoms [3]. These experiences often involve ego dissolution, interconnectedness, and encounters with "teacher" or ancestral presences—phenomena reported across ayahuasca, peyote, and iboga traditions.

Psychologically, the medicines facilitate emotional processing by reducing amygdala reactivity and enhancing prefrontal regulation, enabling safe re-experiencing and reconsolidation of traumatic memories. Participants frequently describe "emotional breakthroughs," resolution of repressed material, and shifts toward greater self-compassion and openness (a Big Five personality trait that remains elevated months later). In ceremonial contexts, these effects are amplified by intention-setting, sacred songs (*icaros* for ayahuasca, drumming for peyote and iboga), and communal witnessing, which provide narrative scaffolding for integration.

Spiritually, many users report enduring increases in self-transcendence, purpose, and connection to something greater than the self—dimensions that Indigenous frameworks view not as epiphenomena but as core therapeutic agents. In the Yaqui and NAC contexts, such experi-

ences reinforce moral clarity, communal responsibility, and alignment with ancestral teachings, contributing to reduced substance misuse and enhanced quality of life.

4.3 Cultural, Relational, and Ecological Mechanisms

Indigenous ontologies frame these medicines as sentient relatives within a kincentric universe. Healing is inherently relational: the plant "teaches" through direct communication, restoring balance among self, community, ancestors, and land. Ceremony provides the essential container—dietary taboos, sacred music, communal support, and post-experience integration—that translates neurobiological plasticity into culturally meaningful change. Without this context, isolated pharmacological effects may be attenuated or even destabilizing [2].

Relational mechanisms operate through multiple channels. Communal witnessing fosters social reconnection and reduces isolation; post-ceremony sharing reinforces new insights within cultural narratives; and ecological reciprocity (e.g., sustainable harvesting, land stewardship) grounds personal healing in collective and environmental responsibility. These elements address the root causes of postcolonial distress—disconnection from culture, land, and ancestors—that Western models often overlook [9]. As articulated in Indigenous consensus frameworks [5], reverence for the plant as kin ensures that healing honors the full web of relationships rather than extracting a single compound.

Empirical support for these mechanisms appears in community-led programs (e.g., Yaqui Intercultural Medicine Clinic), where symptom reductions are comparable to or larger than those reported in decontextualized trials—though no randomized comparison has yet been conducted—suggesting synergy between neuroplasticity and relational repair [8, 14].

4.4 Synthesis and Limitations

The multi-level mechanisms of Indigenous plant medicines—serotonergic/glutamatergic neuroplasticity, mystical/emotional processing, and relational/ecological restoration—offer a comprehensive pathway for mental health that aligns with holistic Indigenous paradigms (Figure 1). Acute pharmacological effects create a window of plasticity; psychological/spiritual experiences provide content for change; and cultural containers ensure integration and durability.

Limitations remain. Most neurobiological data derive from Western laboratory or clinical settings that strip away ceremonial elements. Few studies have employed Indigenous-led designs or culturally specific outcome measures. Mechanistic research on peyote is particularly sparse relative to ayahuasca and iboga. Future work must integrate advanced neuroimaging, biomarkers (e.g., BDNF, inflammation), and mixed-methods approaches that honor relational ontologies to fully capture these medicines' therapeutic potential.

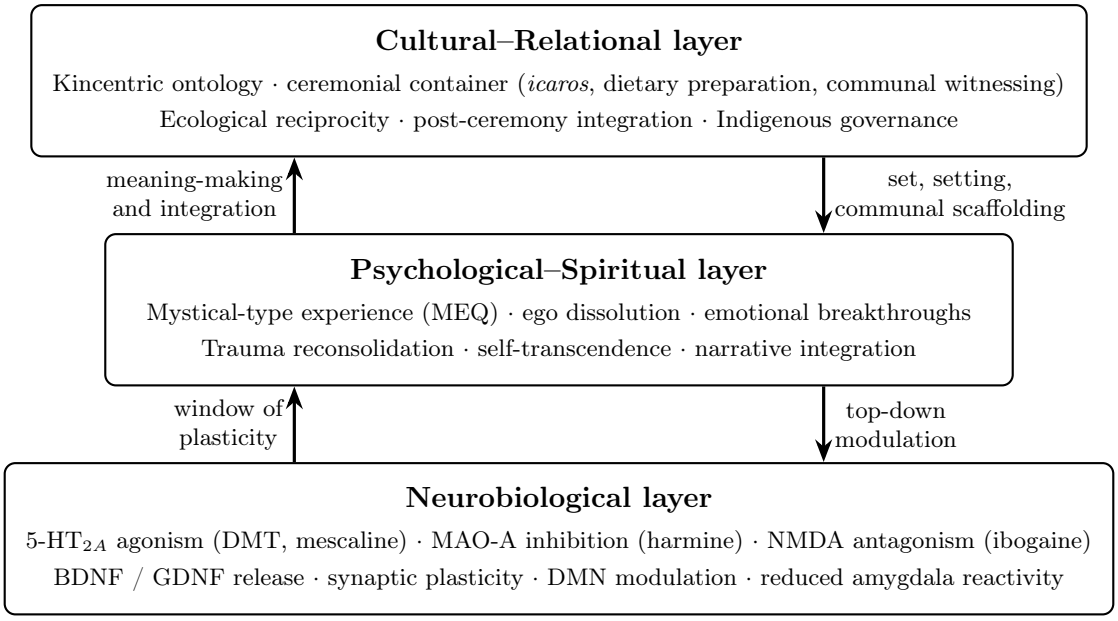

Figure 1: Three-level model of how Indigenous plant medicines support mental health. Bottom-up: pharmacological action opens a window of plasticity that enables mystical and emotional experiences, which in turn become enduring change through cultural integration. Top-down: the ceremonial container shapes set and setting, which in turn shape the subjective experience and modulate the neurobiological response. Decontextualized clinical use removes the top layer.

5 Ethical, Legal, and Practical Challenges

5.1 Cultural Appropriation and Epistemic Injustice

A primary concern is the detachment of plant medicines from their ceremonial, communal, and spiritual contexts. Ayahuasca, peyote, and iboga are not isolated pharmacological tools but "teacher plants" or sacred relatives embedded in specific cultural protocols. When these are commodified in retreat tourism, commercial retreats, or decontextualized clinical trials, the relational and spiritual dimensions critical to healing are often erased. Indigenous participants in global dialogues report feeling excluded from research design, authorship, and decision-making, while their knowledge is mined for patents or profit without attribution. This epistemic injustice perpetuates the marginalization of Indigenous ways of knowing, reducing sophisticated ethnomedical systems to mere "sources" of compounds for Western innovation [2, 5].

5.2 Sustainability and Ecological Impacts

Unsustainable demand driven by global markets threatens the very existence of these medicines and the ecosystems they inhabit. Ayahuasca vine (*Banisteriopsis caapi*) has disappeared from accessible areas of the Amazon, forcing harvesters deeper into primary forest and disrupting traditional supply chains. Peyote (*Lophophora williamsii*) faces extinction risks in parts of its native range due to slow growth, overharvesting, land development, and climate change; Native American Church members increasingly struggle to obtain sufficient sacramental material. Iboga (*Tabernanthe iboga*) in Gabon and surrounding regions suffers from illegal poaching, deforestation, and habitat loss, compounded by export for ibogaine extraction. These pressures not only endanger biodiversity but erode the ecological reciprocity central to Indigenous stewardship, further harming the communities who have protected these plants for millennia.

5.3 Legal and Regulatory Frameworks

Legal landscapes remain fragmented and often inadequate. In the United States, the Native American Church enjoys federal exemptions for peyote use under the American Indian Religious Freedom Act, yet non-Indigenous possession remains restricted. Internationally, ayahuasca and iboga fall under varying controlled-substance schedules, creating barriers to community-led research while permitting commercial exploitation. Attempts to patent traditional varieties (e.g., the 1986 U.S. plant patent on a *Banisteriopsis caapi* strain, revoked in 1999 following challenge by the Coordinating Body of Indigenous Organizations of the Amazon Basin, COICA) exemplify biopiracy. The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits, adopted in 2010 under the Convention on Biological Diversity [16], offers a framework for prior informed consent and benefit-sharing, yet major psychedelic-research nations (e.g., the U.S., Canada) have not ratified it, leaving Indigenous Nations without robust international protections.

5.4 Benefit-Sharing and Economic Justice

Even when research proceeds, benefit-sharing is rare. Profits from pharmaceutical development, retreat centers, and wellness tourism rarely flow back to source communities through royalties, land restoration, or capacity-building. Indigenous leaders emphasize that true reciprocity must include restitution for historical harms—land dispossession, cultural suppression, and intergenerational trauma—rather than token gestures. Without enforceable mechanisms, the economic benefits of plant medicines accrue disproportionately to non-Indigenous entrepreneurs, exacerbating inequities.

5.5 Indigenous-Led Ethical Frameworks

In direct response, a global Indigenous consensus process led by Celidwen et al. [5] produced eight interconnected ethical principles to guide Western engagement with traditional Indigenous medicines. These principles—Reverence, Respect, Responsibility, Relevance, Regulation, Reparation, Restoration, and Reconciliation—form an integrated framework rooted in kincentric worldviews. Table 2 summarizes each principle and its concrete research/policy implications.

Table 2: The eight Indigenous ethical principles for psychedelic research and practice [5], with concrete research and policy implications.

Principle	**Summary**	**Concrete research / policy implication**
Reverence	Acknowledge plants as sacred relatives within a kincentric cosmos.	Treat ceremonial protocols, songs, and prayers as non-fungible context, not as "optional add-ons" in trial design.
Respect	Honor Indigenous sovereignty, protocols, and free prior and informed consent (FPIC).	Require community-level FPIC and Indigenous co-authorship before any data collection or publication.
Responsibility	Be accountable for harms; protect cultural integrity.	Establish Indigenous-led safety boards with authority to pause or terminate trials and retreats.
Relevance	Elevate Indigenous leadership in education, training, and knowledge translation.	Mandate Indigenous mentorship in facilitator-training curricula; fund Indigenous-led pedagogy.
Regulation	Protect tangible (plants, territories) and intangible (songs, ceremonies, knowledge) cultural property.	Prohibit patents on traditional varieties; recognize collective biocultural rights in domestic law.
Reparation	Equitable benefit-sharing including financial and non-financial restitution.	Ratify and operationalize the Nagoya Protocol; route trial revenues into community-controlled funds.
Restoration	Indigenous self-determination, land rights, and cultural revitalization.	Tie research funding to commitments on land return, language revitalization, and healer training.
Reconciliation	Healing colonial legacies through concrete, ongoing action.	Build long-term partnerships measured in decades, not grant cycles; report on power-sharing annually.

These principles are not aspirational checklists but interdependent obligations that must inform every stage of research, policy, and clinical application. Subsequent Indigenous statements and working groups have reinforced them, calling for taskforces, sustainable-harvesting mandates, and community-governed review boards.

5.6 Practical Challenges in Research and Clinical Integration

Implementing these principles in practice presents logistical hurdles. Western protocols often lack culturally attuned screening, integration support, or long-term community follow-up. Training programs for facilitators rarely include Indigenous mentorship, risking unsafe or culturally insensitive sessions. Medicalization can pathologize spiritual experiences, while regulatory demands for RCTs conflict with the relational, non-replicable nature of ceremony. Community-led models (e.g., the Yaqui Intercultural Medicine Clinic) demonstrate feasibility but require sustained funding and policy support that current systems rarely provide. Additional risks include psychological destabilization in unprepared participants and the potential for retraumatization when colonial power dynamics are reproduced in therapeutic settings.

5.7 Synthesis and Pathways Forward

These ethical, legal, and practical challenges are interconnected and cannot be resolved through technical fixes alone. They demand a fundamental shift from extraction to reciprocity, from individual symptom management to relational and ecological restoration. Adopting the eight principles as standard practice—alongside Nagoya Protocol compliance, Indigenous co-governance, and sustainability monitoring—offers a rigorous, justice-oriented path. Failure to do so risks undermining both the therapeutic promise of plant medicines and the sovereignty of the Nations who have stewarded them.

6 Promising Models of Integration and Community-Led Initiatives

This section examines three exemplary models: the Yaqui Intercultural Medicine Clinic, Two-Eyed Seeing frameworks, and conservation-integrated community programs supported by the Indigenous Medicine Conservation Fund.

6.1 The Yaqui Intercultural Medicine Clinic, Sonora, Mexico

The Yaqui Intercultural Medicine Clinic (*Clínica de Medicina Intercultural Yaqui*), established in 2020 in Sonora, Mexico, represents one of the most rigorously documented Indigenous-led integration models. Founded and operated by Yaqui health professionals and traditional healers, the outpatient program serves Yaqui community members experiencing SUDs (particularly methamphetamine), depression, anxiety, complicated grief, PTSD, and suicidality. Treatment integrates ceremonial ayahuasca (and occasionally peyote) within a culturally attuned framework that includes *temazcal* (sweat-lodge) ceremonies, individual and group psychotherapy, community support circles, and ongoing follow-up rooted in Yaqui cosmology and healing traditions.

Preliminary observational data from the ongoing study [8] illustrate striking outcomes. Among 37 participants who completed one or two ayahuasca ceremonies, mean Beck Depression Inventory-II (BDI-II) scores dropped from 15.7 to 5.1; Beck Anxiety Inventory (BAI) scores fell from 16.6 to 6.3; and Inventory of Complicated Grief (ICG) scores decreased from 39.6 to 10.7. Among eight individuals presenting with suicide risk, seven cases resolved after a single ceremony. PTSD symptoms and overall functioning also improved markedly, with changes sustained through follow-up assessments. Safety data were excellent: ayahuasca was well-tolerated, with no serious adverse events reported. Case studies [14] further detail transformative recoveries

from methamphetamine dependence and intergenerational trauma, attributing success to the seamless weaving of plant medicine, Indigenous ritual, and Western psychotherapeutic support.

The clinic explicitly embodies the ethical principles: Yaqui leadership ensures relevance and regulation; ceremonies honor reverence and respect; and program funding models prioritize reparation through community benefit. It demonstrates that Indigenous-governed integration can deliver rapid symptom relief while strengthening cultural identity and communal resilience—outcomes that warrant direct comparison study against non-Indigenous retreat and clinical settings.

6.2 Two-Eyed Seeing (Etuaptmumk) Frameworks in Psychedelic and Mental Health Research

Two-Eyed Seeing, or *Etuaptmumk*, the Mi'kmaw guiding principle articulated by Elders Albert and Murdena Marshall [1], offers a scalable framework for equitable integration across Indigenous Nations. It calls for "learning to see from one eye with the strengths of Indigenous knowledges and ways of knowing, and from the other eye with the strengths of Western knowledges and ways of knowing. . . and learning to use both these eyes together, for the benefit of all." In psychedelic and mental health contexts, Two-Eyed Seeing rejects the supremacy of biomedical reductionism in favor of relational, land-based, and ceremonial approaches while retaining the rigor of Western science for outcome measurement and safety protocols.

Recent applications include neuroscience and brain-health research, where Two-Eyed Seeing challenges deficit-based colonial narratives and incorporates Indigenous perspectives on trauma, suicide prevention, and holistic wellness [12]. In Canadian contexts, it has informed pilot programs combining plant medicines with land-based healing, cultural reclamation, and clinical psychotherapy. For instance, Indigenous researchers have used Two-Eyed Seeing to co-design studies that prioritize community-defined outcomes (e.g., restored kinship relations, land connection) alongside standardized scales. Scoping reviews confirm its growing adoption in Indigenous health research, though authors note the need for fuller methodological transparency to avoid tokenism [20, 21]. When applied to psychedelics, Two-Eyed Seeing ensures that neuroplasticity and mystical experiences are interpreted and integrated through Indigenous ontologies rather than Western individualism.

This framework has inspired hybrid models in Australia, New Zealand, and parts of the United States, where Indigenous health organizations adapt ayahuasca or psilocybin-assisted therapy within cultural safety protocols. Its strength lies in scalability: it provides a practical roadmap for Western institutions to partner respectfully without appropriation.

6.3 Conservation-Integrated and Broader Indigenous-Led Initiatives

The Indigenous Medicine Conservation Fund (IMC Fund) supports a network of community-led projects that link plant-medicine healing directly to biocultural conservation. In the Amazon Basin, partners such as UMIYAC (Union of Indigenous Yagé Medics of the Colombian Amazon) and Shipibo youth programs run "spiritual health brigades," youth training in ancestral knowledge, and forest expeditions led by *sabedoras* (grandmother knowledge keepers). These initiatives combine ayahuasca-based healing with territorial defense and sustainable harvesting, directly addressing mental health while countering overexploitation.

In Gabon, Blessings of the Forest (BOTF) empowers Bwiti and Pygmy communities to cultivate iboga, establish fair-trade protocols under the Nagoya Protocol, and strengthen healer associations. The first Nagoya-compliant iboga exports (2023) demonstrate how benefit-sharing can fund community mental health programs while protecting the plant. Similarly, the Indigenous Peyote Conservation Initiative works with over 45 U.S. tribes to repopulate peyote gardens, secure land access, and maintain Native American Church ceremonial supply, ensuring the medicine remains available for intergenerational trauma healing.

Additional models include Chacruna Institute's Indigenous Reciprocity Initiative of the Americas, which redirects philanthropic resources to small Indigenous organizations, and calls for a Global Indigenous Council to guide policy. These efforts illustrate that true integration must be reciprocal: conservation and cultural revitalization are not side projects but core components of mental health care.

6.4 Synthesis and Lessons for Scalable Integration

Common threads across these models include Indigenous governance, ceremonial integrity, community integration, ecological stewardship, and outcome measures that honor relational well-being. They achieve rapid, clinically meaningful improvements while advancing sovereignty and sustainability—outcomes that validate the ethical principles and multi-level mechanisms discussed earlier. Challenges remain: funding instability, regulatory barriers, and the need for larger-scale evaluation. Nevertheless, these initiatives provide replicable blueprints for respectful collaboration.

7 Future Directions and Recommendations

The recommendations below are organized as priorities for Indigenous-led research, policy and regulation, education and training, scaling community-led models, sustainability and conservation, and global governance, structured around the eight ethical principles [5] and Two-Eyed Seeing [1].

7.1 Prioritizing Indigenous-Led Research and Culturally Attuned Methodologies

Research agendas must move beyond Western-centric RCTs that isolate compounds and decontextualize ceremony. Indigenous-governed studies should employ mixed-methods designs that integrate quantitative clinical outcomes (e.g., depression, PTSD scales) with qualitative, relational, and community-defined measures, such as restored kinship bonds, land connection, cultural continuity, and spiritual well-being. Two-Eyed Seeing provides an ideal methodological scaffold: one eye honors Indigenous epistemologies (e.g., ceremonial data collection, oral histories, and visionary insight), while the other applies rigorous Western tools (e.g., longitudinal neuroimaging, biomarkers like BDNF, and ecological impact assessments).

Key priorities include:

- Funding streams dedicated to Indigenous-led consortia (e.g., expanding the Indigenous Medicine Conservation Fund model to support multi-year RCTs within Yaqui-style clinics).
- Development of culturally validated outcome instruments co-created with participating Nations.
- Longitudinal studies tracking intergenerational effects, including youth mental health and cultural revitalization.
- Open-access data repositories governed by Indigenous data sovereignty principles (e.g., CARE: Collective benefit, Authority to control, Responsibility, Ethics).

Such research will fill critical gaps in efficacy data for peyote and iboga while strengthening the evidence base for ayahuasca in SUDs and trauma [24].

7.2 Policy and Regulatory Reforms

Current legal frameworks often criminalize or marginalize traditional use while enabling commercial exploitation. Policymakers should pursue:

- Ratification and implementation of the Nagoya Protocol [16] by all nations engaged in psychedelic research, with mandatory benefit-sharing agreements tied to FPIC.
- Expansion of religious and cultural exemptions (modeled on the U.S. American Indian Religious Freedom Act) to additional Indigenous Nations and international contexts.
- Creation of "plant medicine sovereignty zones" or regulatory sandboxes that allow community-led programs to operate under Indigenous governance while meeting basic safety standards.
- National and international taskforces (co-chaired by Indigenous knowledge holders) to draft guidelines for clinical integration, patent prohibitions on traditional varieties, and sustainable trade standards.

These reforms must be accompanied by reparative funding: governments and philanthropic organizations should allocate resources proportional to historical harms, supporting land return, language revitalization, and healer training as integral components of mental health infrastructure.

7.3 Education, Training, and Capacity Building

Western psychedelic training programs must be decolonized. Recommendations include:

- Mandatory Indigenous mentorship requirements for facilitators, therapists, and researchers.
- Development of dual-certification curricula that teach both clinical safety protocols and ceremonial ethics, reverence, and relational care.
- Scholarships and leadership pipelines for Indigenous students and healers to enter psychedelic science and policy arenas.
- Public education campaigns that accurately represent plant medicines as sacred relatives rather than novel therapeutics, countering spiritual consumerism and retreat-tourism hype.

Two-Eyed Seeing should become a core competency in medical, psychological, and public-health training, ensuring future practitioners can hold both knowledge systems with humility and rigor.

7.4 Scaling Promising Community-Led Models

Programs such as the Yaqui Intercultural Medicine Clinic offer replicable blueprints. Future efforts should focus on:

- Technical and financial support for additional Indigenous Nations to establish intercultural clinics, adapting the Yaqui model to local medicines (e.g., peyote in North America, iboga in Central Africa).
- Hybrid service-delivery networks that combine outpatient ceremonies with telehealth integration, land-based healing, and primary-care collaboration.
- Evaluation frameworks that track not only symptom reduction but also community resilience metrics (e.g., reduced suicide clusters, strengthened governance, ecological restoration).
- Pilot "Two-Eyed Seeing hubs" in urban Indigenous communities and rural territories to address accessibility barriers for displaced or diaspora populations.

7.5 Sustainability and Biocultural Conservation

Plant medicines cannot be separated from their ecosystems. Immediate actions include:

- Global moratoriums on commercial wild harvesting until sustainable cultivation and fair-trade protocols are established.
- Investment in Indigenous-led conservation initiatives (e.g., peyote gardens, iboga agroforestry, ayahuasca agroecology) linked directly to mental-health funding.
- Climate-adaptive stewardship plans co-developed with knowledge keepers to protect habitats amid environmental change.

Conservation must be framed as relational healing: protecting the plants protects the mental and spiritual health of the peoples who steward them.

7.6 Global Collaboration and Governance Structures

A permanent Global Indigenous Council on Plant Medicines (modeled on existing working groups and inclusive of diverse Nations) should be established to advise the United Nations, World Health Organization, and research funders. This body would:

- Oversee ethical review of international projects.
- Facilitate knowledge exchange between Amazonian, North American, African, and Oceanic traditions.
- Monitor compliance with the eight principles and Nagoya obligations.

Inter-Indigenous solidarity networks can accelerate best-practice sharing while protecting against external appropriation.

7.7 Synthesis and Call to Action

The path forward is clear: plant medicines will realize their full potential for mental health only when Indigenous leadership, the eight ethical principles, and Two-Eyed Seeing become non-negotiable standards. This requires shifting resources, rewriting policies, redesigning research, and rebuilding relationships damaged by colonialism. By investing in these directions, Western institutions and practitioners can move from extraction to reciprocity, contributing meaningfully to decolonization and global mental health equity. The responsibility now lies with researchers, funders, policymakers, and clinicians to act with urgency, humility, and accountability.

8 Conclusion

Indigenous plant medicines—ayahuasca, peyote, and iboga—embody millennia of sophisticated, relational healing technologies that address dimensions of mental distress which Western biomedical models often leave unaddressed. As this review has demonstrated, these sacred relatives operate within holistic, kincentric worldviews that view health as dynamic balance among mind, body, spirit, community, ancestors, and land. When used in their proper ceremonial contexts, they produce rapid, clinically meaningful, and often sustained reductions in depression, anxiety, PTSD, substance use disorders, and suicidality. Longitudinal and community-based studies document moderate-to-large effect sizes, neuroplastic changes, mystical-type experiences, and relational restoration that together are at least comparable in magnitude to many conventional interventions, with the durability of effect being a particular strength. Yet these outcomes are inseparable from the cultural containers that give them meaning: the dietary protocols, sacred

songs, communal witnessing, and ecological reciprocity that amplify neurobiological plasticity and translate insight into enduring life change.

The contemporary psychedelic renaissance has brought unprecedented visibility and funding to these substances, yet it has too often replicated colonial patterns of extraction—detaching active compounds from their Indigenous origins, excluding traditional knowledge holders from leadership and benefit-sharing, and commodifying sacred practices for retreat tourism or pharmaceutical profit. This paper has foregrounded the ethical, legal, and practical challenges that arise when such extraction occurs: cultural appropriation, epistemic injustice, unsustainable harvesting, and the erosion of the very relational mechanisms that underpin therapeutic success. In response, Indigenous-led consensus has provided a clear, actionable roadmap through the eight interconnected principles—Reverence, Respect, Responsibility, Relevance, Regulation, Reparation, Restoration, and Reconciliation. These principles are not optional add-ons but foundational requirements for any ethical engagement with plant medicines.

Promising models such as the Yaqui Intercultural Medicine Clinic demonstrate that when Indigenous governance, Two-Eyed Seeing (*Etuaptmumk*), and the eight principles are centered, integration yields transformative results: dramatic symptom relief, cultural revitalization, and community resilience. Conservation-linked initiatives further show that mental health healing and biocultural stewardship are inseparable. The future directions outlined in Section 7—Indigenous-led research agendas, policy reform, decolonized training, scalable community models, and global governance structures—offer a practical pathway to move from extraction to reciprocity.

Realizing this vision demands urgent, systemic action. Researchers, funders, clinicians, and policymakers must commit to Indigenous sovereignty as the non-negotiable foundation of all work involving these medicines. This includes ratifying and implementing the Nagoya Protocol, establishing Indigenous-governed review boards, redirecting resources toward reparation and restoration, and embedding Two-Eyed Seeing across training and service delivery. Only through such reciprocity can the psychedelic renaissance evolve into a genuinely decolonial movement—one that honors the plants as kin, protects the territories and knowledge systems that have sustained them, and contributes meaningfully to global mental health equity.

The stakes extend beyond individual symptom relief. Postcolonial distress, ecological collapse, and spiritual disconnection are intertwined crises. Plant medicines, when stewarded respectfully, offer pathways to heal these interconnected wounds. By restoring relationships—to self, community, ancestors, land, and the living world—they model the kind of holistic transformation our times require. Western science and practice now face a choice: continue patterns of appropriation that diminish both the medicines and the peoples who have protected them for millennia, or embrace humility, accountability, and partnership to co-create mental health systems worthy of the relational intelligence these teacher plants embody.

In closing, we reaffirm that the true power of Indigenous plant medicines lies not in their molecular structure alone but in the sacred relationships they nurture. May future research, policy, and practice be guided by the eight principles, Two-Eyed Seeing, and the voices of the Nations who have stewarded these medicines since time immemorial. Only then can plant medicines fulfill their potential to support mental, emotional, spiritual, and ecological well-being—for Indigenous communities and for humanity as a whole.

References

[1] Bartlett, C., Marshall, M., & Marshall, A. (2012). Two-Eyed Seeing and other lessons learned within a co-learning journey of bringing together indigenous and mainstream knowledges and ways of knowing. *Journal of Environmental Studies and Sciences*, 2(4), 331–340. doi:10.1007/s13412-012-0086-8

[2] Bouso, J. C., & Sánchez-Avilés, C. (2020). Traditional healing practices involving psychoac-

tive plants and the global mental health agenda. *Health and Human Rights Journal*, 22(1), 145–150.

[3] Brown, R. E., Anker, J. J., Cherian, K. N., et al. (2025). Mystical experiences during magnesium–ibogaine are associated with improvements in PTSD symptoms in veterans. *Journal of Affective Disorders*, 395 (Part B), 120722. doi:10.1016/j.jad.2025.120722

[4] Bruhn, J. G., De Smet, P. A. G. M., El-Seedi, H. R., & Beck, O. (2002). Mescaline use for 5700 years. *The Lancet*, 359(9320), 1866. doi:10.1016/S0140-6736(02)08701-9

[5] Celidwen, Y., Redvers, N., Githaiga, C., Calambas, J., Allkins, K., Chindoy, M. E., Vitale, R., Rojas, J. N., Mondragón, D., Rosalio, Y. V., & Sacbajá, A. (2023). Ethical principles of traditional Indigenous medicine to guide western psychedelic research and practice. *The Lancet Regional Health – Americas*, 18, 100410. doi:10.1016/j.lana.2022.100410

[6] Cherian, K. N., Keynan, J. N., Anker, L., Faerman, A., Brown, R. E., Shamma, A., Keynan, O., Coetzee, J. P., Batail, J.-M., Phillips, A., Bassano, N. J., Sahlem, G. L., Inzunza, J., Millar, T., Dickinson, J., Rolle, C. E., Keller, J., Adamson, M., Kratter, I. H., & Williams, N. R. (2024). Magnesium–ibogaine therapy in veterans with traumatic brain injuries. *Nature Medicine*, 30(2), 373–381. doi:10.1038/s41591-023-02705-w

[7] Fábregas, J. M., González, D., Fondevila, S., Cutchet, M., Fernández, X., Barbosa, P. C. R., Alcázar-Córcoles, M. Á., Barbanoj, M. J., Riba, J., & Bouso, J. C. (2010). Assessment of addiction severity among ritual users of ayahuasca. *Drug and Alcohol Dependence*, 111(3), 257–261. doi:10.1016/j.drugalcdep.2010.03.024

[8] Giovannetti, C., Castillo Valenzuela, T., Loizaga-Velder, A., Campoy Gómez, R., Ochoa Jaime, G. R., Sanchez, G., Marcus, O., Agin-Liebes, G., & Rush, B. (2024). Preliminary results from a community-based ayahuasca-assisted mental health program among a Yaqui Indigenous population in Sonora, Mexico. *Journal of Psychedelic Studies*, 8(3). doi:10.1556/2054.2024.00401

[9] Gone, J. P. (2021). The (post)colonial predicament in community mental health services for American Indians: Explorations in alter-Native psy-ence. *American Psychologist*, 76(9), 1514–1525. doi:10.1037/amp0000906

[10] Halpern, J. H., Sherwood, A. R., Hudson, J. I., Yurgelun-Todd, D., & Pope, H. G., Jr. (2005). Psychological and cognitive effects of long-term peyote use among Native Americans. *Biological Psychiatry*, 58(8), 624–631. doi:10.1016/j.biopsych.2005.06.021

[11] Hamill, J., Hallak, J., Dursun, S. M., & Baker, G. (2019). Ayahuasca: Psychological and physiologic effects, pharmacology and potential uses in addiction and mental illness. *Current Neuropharmacology*, 17(2), 108–128. doi:10.2174/1570159X16666180125095902

[12] Illes, J., & Perreault, M. L. (2025). Two-Eyed Seeing and other Indigenous perspectives for neuroscience. *Nature*, 638, 58–66. doi:10.1038/s41586-024-08437-2

[13] Jiménez-Garrido, D. F., Gómez-Sousa, M., Ona, G., Dos Santos, R. G., Hallak, J. E. C., Alcázar-Córcoles, M. Á., & Bouso, J. C. (2020). Effects of ayahuasca on mental health and quality of life in naïve users: A longitudinal and cross-sectional study combination. *Scientific Reports*, 10(1), 4075. doi:10.1038/s41598-020-61169-x

[14] Loizaga-Velder, A., Giovannetti, C., & Castillo Valenzuela, T. (2023). Therapeutic effects of ceremonial ayahuasca use for methamphetamine use disorders and other mental health challenges: Case studies in an Indigenous community in Sonora, Mexico. *Journal of Psychoactive Drugs*, 55(5), 600–610. doi:10.1080/02791072.2023.2255182

[15] Lowe, M. X., Kettner, H., Jain, S., Kaur, R., Husain, M. I., & Roseman, L. (2024). Long-term benefits to psychological health and well-being after ceremonial use of ayahuasca in Middle Eastern and North African immigrants and refugees. *Frontiers in Psychiatry*, 15, 1279887. doi:10.3389/fpsyt.2024.1279887

[16] Secretariat of the Convention on Biological Diversity. (2011). *Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity*. United Nations Environment Programme. https://www.cbd.int/abs/

[17] Osório, F. de L., Sanches, R. F., Macedo, L. R., Santos, R. G. dos, Maia-de-Oliveira, J. P., Wichert-Ana, L., Araujo, D. B. de, Riba, J., Crippa, J. A. S., & Hallak, J. E. C. (2015). Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: A preliminary report. *Brazilian Journal of Psychiatry*, 37(1), 13–20. doi:10.1590/1516-4446-2014-1496

[18] Pagni, B. A., Sarris, J., Perkins, D., et al. (2025). Long-term mental health and wellbeing outcomes associated with naturalistic ayahuasca consumption. *Journal of Psychoactive Drugs*, advance online publication. doi:10.1080/02791072.2025.2465800

[19] Perkins, D., Opaleye, E. S., Simonova, H., Bouso, J. C., Tofoli, L. F., Galvão-Coelho, N. L., Schubert, V., & Sarris, J. (2022). Changes in mental health, wellbeing and personality following ayahuasca consumption: Results of a naturalistic longitudinal study. *Frontiers in Pharmacology*, 13, 884703. doi:10.3389/fphar.2022.884703

[20] Roher, S. I. G., Yu, Z., Martin, D. H., & Benoit, A. C. (2021). How is Etuaptmumk/Two-Eyed Seeing characterized in Indigenous health research? A scoping review. *PLOS ONE*, 16(8), e0254612. doi:10.1371/journal.pone.0254612

[21] Roher, S. I. G., Martin, D. H., Benoit, A. C., & Yu, Z. (2024). How Etuaptmumk/Two-Eyed Seeing is used in Indigenous health research: A scoping review. *PLOS ONE*, 19(9), e0310247. doi:10.1371/journal.pone.0310247

[22] Ruffell, S. G. D., Netzband, N., Tsang, W., Davies, M., Butler, M., Rucker, J. J. H., Tofoli, L. F., Dempster, E. L., Young, A. H., & Morgan, C. J. A. (2021). Ceremonial ayahuasca in Amazonian retreats—Mental health and epigenetic outcomes from a six-month naturalistic study. *Frontiers in Psychiatry*, 12, 687615. doi:10.3389/fpsyt.2021.687615

[23] Ruffell, S. G. D., Crosland-Wood, M., Palmer, R., Netzband, N., Tsang, W., Weiss, B., Gandy, S., Cowley-Court, T., Halman, A., McHerron, D., Jong, A., Kennedy, T., White, E., Perkins, D., Terhune, D. B., & Sarris, J. (2023). Ayahuasca: A review of historical, pharmacological, and therapeutic aspects. *Psychiatry and Clinical Neurosciences Reports*, 2(4), e146. doi:10.1002/pcn5.146

[24] Rush, B., Marcus, O., Garcia, S., Loizaga-Velder, A., Loewinger, G., Spitalier, A., & Mendive, F. (2022). *Psychedelic Medicine: A Rapid Review of Therapeutic Applications and Implications for Future Research*. Homewood Research Institute / Queen's University, Canada.

[25] Sarris, J., Perkins, D., Cribb, L., Schubert, V., Opaleye, E., Bouso, J. C., Scheidegger, M., Aicher, H., Suzuki, J., Tofoli, L. F., et al. (2021). Ayahuasca use and reported effects on depression and anxiety symptoms: An international cross-sectional study of 11,912 consumers. *Journal of Affective Disorders Reports*, 4, 100098. doi:10.1016/j.jadr.2021.100098

[26] Sheth, R., Parikh, E., Olayeye, K., Pfeifer, K., & Khanna, D. (2024). The effects of ayahuasca on psychological disorders: A systematic literature review. *Cureus*, 16(3), e55574. doi:10.7759/cureus.55574

[27] Talin, P., & Sanabria, E. (2017). Ayahuasca's entwined efficacy: An ethnographic study of ritual healing from "addiction". *International Journal of Drug Policy*, 44, 23–30. doi:10.1016/j.drugpo.2017.02.017

[28] Turner, V. (1969). *The Ritual Process: Structure and Anti-Structure*. Aldine de Gruyter, Chicago.

[29] Vorobyeva, N., & Kozlova, A. A. (2022). Three naturally-occurring psychedelics and their significance in the treatment of mental health disorders. *Frontiers in Pharmacology*, 13, 927984. doi:10.3389/fphar.2022.927984

[30] World Health Organization. (2022). *World Mental Health Report: Transforming Mental Health for All*. World Health Organization, Geneva. https://www.who.int/publications/i/item/9789240049338