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CHEMISTRY AND PHARMACOLOGY | REVIEW

Potential therapeutic use of ayahuasca: A literature review

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ABSTRACT

Ayahuasca is a psychoactive decoction originally used in indigenous Amazonian culture. It consists of a dense brown liquid that most frequently results from the decoction of two plants native to the Amazon rainforest, *Psychotria viridis* (Rubiaceae) and *Banisteriopsis caapi* (Malpighiaceae). The composition of the decoction is variable, as several plant species can be used in its preparation. Its psychoactive effect occurs due to the presence of N,N-dimethyltryptamine (DMT), an agonist at serotonergic receptors (5-$HT_{1A/2A/2C}$) that is metabolized by the enzyme monoamine oxidase type A (MAO-A), and also the presence of β-carbolines, which are reversible MAO-A inhibitors. This joint interaction promotes a sequence of psychedelic neurochemical effects. Due to the current expansion of research on psychedelic substances and the growing public interest in the benefits of ayahuasca beyond its traditional use in the Amazon, academic research on its therapeutic capacity has been increasing. This study aimed to carry out a literature review on the scientific evidence for the therapeutic potential of ingesting ayahuasca. The review covered the period 2012-2022, and resulted in evidence on the therapeutic effects of ayahuasca on depression/anxiety, chemical dependency/alcoholism and Parkinson's disease, as well as neuropsychological effects, and possible toxic effects on reproduction/embryonic development, among other adverse effects. The highest number of publications in the searched period dealt with the effects of ayahuasca on depression and anxiety. Further studies need to address the detailed mechanism of action of ayahuasca, as well as its potential toxicity, in order to demonstrate its safety.

KEYWORDS: *Psychotria viridis*; *Banisteriopsis caapi*; medicinal effects; *N,N*-dimethyltryptamine

Potencial uso terapêutico da ayahuasca: Uma revisão da literatura

RESUMO

Ayahuasca é uma decocção psicoativa originalmente usada na cultura indígena amazônica. É constituída por um líquido denso e marrom que resulta mais frequentemente da decocção de duas plantas nativas da floresta amazônica, *Psychotria viridis* (Rubiaceae) e *Banisteriopsis caapi* (Malpighiaceae). A composição da decocção é variável, pois diversas espécies vegetais podem ser utilizadas em seu preparo. Seu efeito psicoativo ocorre devido à presença de N,N-dimetiltriptamina (DMT), agonista dos receptores serotoninérgicos (5-$HT_{1A/2A/2C}$), que é metabolizado pela enzima monoamina oxidase tipo A (MAO-A), e também à presença de β-carbolinas, que são inibidores reversíveis da MAO-A. Essa interação conjunta promove uma sequência de efeitos neuroquímicos psicodélicos. Devido à atual expansão das pesquisas sobre substâncias psicodélicas e ao crescente interesse público nos benefícios da ayahuasca, além do seu uso tradicional na Amazônia, as pesquisas acadêmicas sobre sua capacidade terapêutica têm aumentado. Este estudo teve como objetivo realizar uma revisão de literatura sobre as evidências científicas do potencial terapêutico da ingestão de ayahuasca. A revisão abrangeu o período 2012-2022, e resultou em evidências sobre os efeitos terapêuticos da ayahuasca na depressão/ansiedade, dependência química/alcoolismo e doença de Parkinson, bem como efeitos neuropsicológicos, e possíveis efeitos tóxicos na reprodução/desenvolvimento embrionário, entre outros efeitos adversos. O maior número de publicações no período pesquisado tratou dos efeitos da ayahuasca sobre a depressão e a ansiedade. Estudos futuros precisam abordar o mecanismo detalhado de ação da ayahuasca, bem como sua potencial toxicidade, a fim de demonstrar sua segurança.

PALAVRAS-CHAVE: *Psychotria viridis*; *Banisteriopsis caapi*; efeitos medicinais; *N,N*-dimetiltriptamina

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INTRODUCTION

Ayahuasca is a psychoactive decoction most frequently composed of two plant species native to the Amazon rainforest: the vine *Banisteriopsis caapi* Callaway and Grob 1998 (Malpighiaceae) and the leaves of the shrub *Psychotria viridis* Ruiz & Pavon 1799 (Rubiaceae) (Daldegan-Bueno *et al*. 2023; Gonçales *et al*. 2023) (Figure 1). Ayahuasca is traditionally used for ritual purposes by the indigenous population of the Amazon region and began to be used in Brazil since the 20th century as a legally regulated sacrament in rituals for different syncretic religious organizations such as Santo Daime, União do Vegetal (UDV) and Barquinha (Labate and MacRae 2016). Over the last decades, ayahuasca use has spread to other countries, where it is legally employed in ayahuasca retreat centers and neoshamanic groups (Garrido *et al*. 2020), as well as a growing number of religious groups and alternative therapy centers (Brito-da-Costa *et al*. 2020).

Banisteriopsis caapi contains phytochemicals from the β-carboline class, such as harmine, harmaline and tetrahydroharmine, alkaloids from the class of the monoamine oxidase A inhibitors (IMAO), responsible for the metabolization of the catecholamines. The leaves of *P. viridis* contain the potent psychedelic alkaloid *N*,*N*-dimethyltryptamine (DMT) (Table 1). DMT is structurally similar to serotonin, and serotonergic receptors are the main targets of psychedelic molecules such as LSD, psilocybin, mescaline and DMT itself (Hanks and González-Maeso 2013; Jaster *et al*. 2022). DMT alone is not psychoactive after oral administration, but in ayahuasca the reversible inhibition of peripheral MAO-A by β-carbolines present in other components of the decoction allows DMT to reach the central nervous system by binding to 5-HT_{1A}, 5- HT_{2A} and 5-HT_{2C} receptors (Keiser *et al*. 2009; Kaasik *et al*. 2021).

The therapeutic potential of ayahuasca has been reported for diverse psychiatric conditions, such as alcohol and nicotine addiction, other drug abuses, and the treatment of depression cases (e.g., Hamill *et al*. 2019; Orsolini *et al*. 2020). Ayahuasca has also been evaluated and used for treatment of neurodegenerative diseases such as Parkinson's disease (Bezerra 2020). In this context, considering the growing interest in scientific research on the therapeutic properties and potential harm of psychedelic substances, in particular of ayahuasca, we aimed to review publications on the pharmacological properties of ayahuasca over the last decade.

MATERIAL AND METHODS

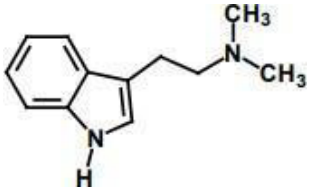
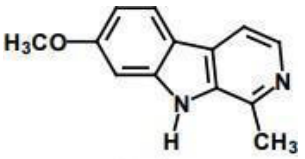
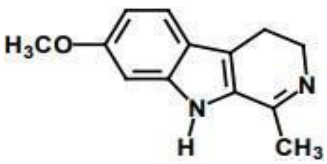
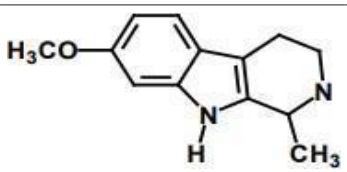
This is a narrative review of published studies on the therapeutic use of ayahuasca. We surveyed articles in the databases of Web of Science, Scielo, PUBMED and ScienceDirect. The following search terms and their combinations in Portuguese and English were used: ayahuasca, therapeutic use, therapeutic potential and toxic effects.

The inclusion criteria were: articles published in Portuguese and English; full articles on therapeutic uses of ayahuasca performed in animal models and/or humans from 2012 to 2022. Review articles, non free-access articles, theses, books and grey documents were excluded from the search results. Articles that were judged not to include relevant information on the search terms were also excluded.

Eligible articles were evaluated for duplicity and had their full text analyzed for title and abstract, then, the relevance and relationship between the search terms and the objectives proposed. The synthesis of the data collected from the articles was descriptive and was organized by therapeutic purposes (Figure 2).

Figure 1. Floral variation in morphotypes of *Banisteriopsis caapi* (A, B) and the leaves and stem of the shrub *Psychotria viridis* (C). Credit: Thévenin (2017) and J.K.M. Barreto.

Table 1. Characterization of substances present in formulations of ayahuasca decoctions.

Substance	Chemical structure	Molecular formula	Classification	Structural similarity	Mechanism of action
Dimethyltryptamine (DMT)		$C_{12}H_{16}N_2$	Indole alkaloid with psychedelic effects	Similar to serotonin and melatonin, derivatives of the amino acid tryptophan. Chemical structure similar to sumatriptan (Schripsema and Dagnino 2017)	Non-selective serotonin receptor agonist (Brito-da-Costa et al. 2020)
Harmine (HRM)		$C_{13}H_{12}N_2O$	β-carboline	Similar to indole amines such as serotonin (Schripsema and Dagnino 2017)	MAO inhibitors (inhibit the intestinal desamination of DMT, allowing it to reach the brain). Increase in serotonin, dopamine and norepinephrine levels in the brain. (Brito-da-Costa et al. 2020)
Harmaline (HRL)		$C_{13}H_{14}N_2O$	β-carboline		
Tetrahydroharmine (THH)		$C_{13}H_{16}N_2O$	β-carboline		Serotonin reuptake transporter inhibitor (Brito-da-Costa et al. 2020)

SURVEY RESULTS

The preliminary search identified 1271 documents (Figure 2). After application of the exclusion criteria and the exclusion of duplicated documents, 20 articles were eligible for full text analysis, including observational, pre-clinical and clinical studies that reported therapeutic effects of ayahuasca as well as analysis of component substances (Table 2). Some articles were divided in more than one study, such as the article published by Pic-Taylor *et al*. (2015), Andrade *et al*. (2018) e Motta *et al*. (2018), as they assessed more than one ayahuasca effect, combining toxicity with behavioral assessment or embryonic development.

The report on the articles was organized according to four therapeutic fields: depression/anxiety, chemical dependency/alcoholism, parkinson's disease, and neuropsychological effects and possible toxic effects (reproduction/embryonic development and adverse effects) (Figure 3). Neuropsychological effects included studies on the effect of ayahuasca on memory, mourning, suicidal tendency, mental health and conciousness state. In the surveyed period, a larger number of articles was published about the effects of ayahuasca on depression and anxiety (Figure 3).

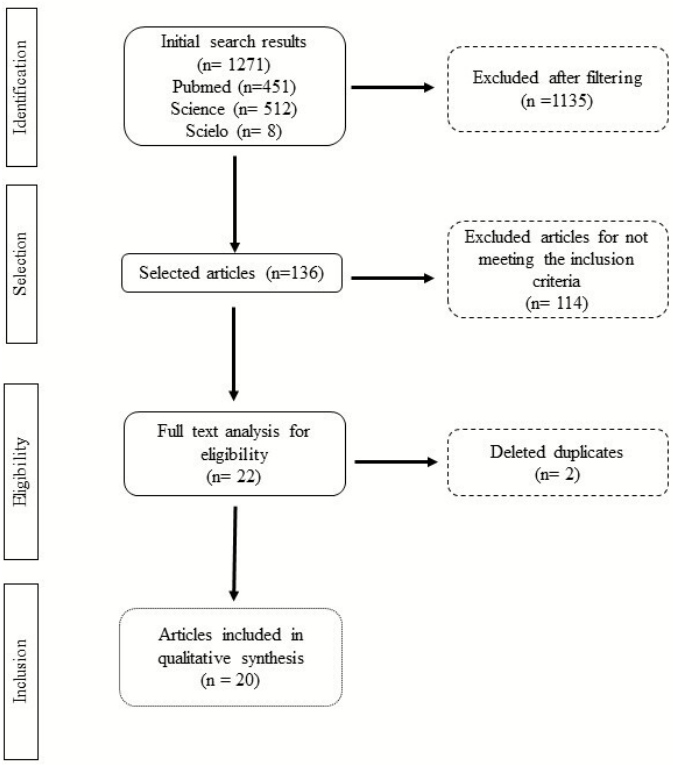


Figure 2. Search strategy summary flowchart.

Table 2. Summary of the main therapeutic effects of ayahuasca (AYA) use observed in 20 studies resulting from our literature review. DMT = *N,N*-dimethyltryptamine; HRM = harmine; HRL = harmaline; THH = tetrahydroharmine; (-) = not described in the study.

Evaluated aspect	Type of study	Effects	Identified substances	Concentration (mg mL^{-1})	Source
Acute effects on neuropsychological performance (memory)	Clinical trial	Mixed effects, negatively affecting work memory, but not interfering with stimulus response.	-	-	Bouso *et al*. (2013)
Toxicity and behavioral functions	Animal models (rats)	Decrease in locomotor activity and activation of brain areas involved in interpretation and emotional process.	-	-	Pic-Taylor *et al*. (2015)
Alcoholism	Animal models	Inhibition in ethanol-induced hyperlocomotion.	-	-	Oliveira-Lima *et al*. (2015)
Depression	Open preliminary study	Significant and fast reduction of depressive symptoms and hopelessness.	DMT HRM	0.8 0.21	Osório *et al*. (2015)
Depression	Clinical trial	Increase in brain blood perfusion and fast sustained antidepressive effects regardless of severity of patient current depressive episode.	DMT HRM	0.8 0.21	Sanches *et al*. (2016)
Effects on animal reproduction	Animal models (rats)	Significant increase in total serum testosterone, decrease in spermatic transit time and spermatic reserves in the epididymis caudae with 4× dose (13.2 mg kg^{-1} harmine, 1.04 mg kg^{-1} harmaline, 1.24 mg kg^{-1} DMT), but not with highest dose. No significant changes in other reproductive endpoints (spermatozoid motility and morphology, total spermatozoid count, daily sperm production), and histology of testis and epididymis.	DMT HRM HRL	0.146 1.56 0.12	Santos *et al*. (2017)
Chemical dependency	Qualitative ethnographic analysis	Effectiveness in treatment of substance dependency was demonstrated.	-	-	Talin and Sanabriab (2017)
Toxicity and behavioral evaluation	Animal models (zebrafish)	Anomalies in embryos at highest concentration, including hatching delay, loss of equilibrium, edema and accumulation of red blood cells. Embryo significantly decreased locomotor activity.	DMT HRM HRL	0.141 1.56 0.122	Andrade *et al*. (2018)
Fetal toxicity and embryonic development	Animal models (rats)	50% mortality at higher doses, and neuronal loss, kidney injuries, intrauterine growth retardation, embryo death and anomalies in fetuses.	DMT HRM HRL	0.141 1.56 0.122	Motta *et al*. (2018)
Depression	Animal models	Behavioral and physiological improvements. Increase in cortisol levels (hormone involved in depression etiology).	DMT HRM HRL THH	0.01 0.11 0.03 0.05	Silva *et al*. (2019)
Depression	Double- blinded placebo-controlled study	Rapid antidepressant effect after single dosing session compared with placebo. Depression severity changed significantly but differently for ayahuasca and placebo groups. Significantly higher improvement in psychiatric scales in the ayahuasca group compared to placebo at all time points.	DMT HRM HRL THH	0.01 0.11 0.24 0.05	Palhano-Fontes *et al*. (2019)
Prolonged grief disorder	Observational study (no control)	Significant decrease in grief symptoms and severity with ceremonial use. Improvement in psychosocial well-being. Participants responded to online survey that included the Texas Revised Inventory of Grief, Symptom Assessment-45, WHO Quality of Life-Bref, Acceptance and Action Questionnaire, and Decentering.	DMT HRM HRL THH	2.0 2.0 0.37 1.0	Gonzales *et al*. (2020)
Suicidal tendency in individuals with major depressive disorder (MDD)	Open-label trial	Rapid and sustained reductions in suicidality among individuals with major depressive disorder (MDD). Decrease in suicidality highest 21 days after intervention.	DMT HRM	0.8 0.21	Zeifman *et al*. (2020)
Inflammatory biomarkers of depression	Double- blinded placebo-controlled study	Significant reduction of C-reactive protein levels across time in patients and controls, but not in placebo. Significant correlation between decrease in C-reactive protein and decrease in depressive symptoms 48 h after substance ingestion (Montgomery-Åsberg Depression Rating Scale).	DMT HRM HRL THH	0.36 1.86 0.24 1.20	Galvao-Coelho *et al*. (2020)
Mental health	Observational study	Associatuon of mental health with non-pharmacological factors that cause placebo response and dose-dependent pharmacological contribution of AYA.	DMT HRM HRL	2.01 5.57 0.38	Uthaug *et al*. (2021)
Adverse effects	Transversal study	Mild and tolerable adverse effects in individuals after AYA use, pending care with drug interactions.	-	-	Durante *et al*. (2021)

Table 2. Continued.

Evaluated aspect	Type of study	Effects	Identified substances	Concentration (mg mL^{-1})	Source
Depression and anxiety	Observational study	Most participants believed that they were cured or became better after AYA ingestion. A small part reported worsening of the symptoms.	-	-	Sarris *et al*. (2021)
State of conciousness	Observational study	Unbalance in circulating concentrations of aromatic amino acids involved in neurotransmission.	DMT HRM HRL THH	0.14 4.5 0.51 2.10	Madrid-Gambin *et al*. (2022)
Chemichal dependency	Animal models	Increase in locomotor activity relative to control during acquisition of sensitization.	DMT	1.76 mg kg^{-1}	Almeida *et al*. (2022)
Parkinson's disease	*In vitro* model	MAO inhibitory activity by β-carbolines with potential to treat parkinsonism due to dopamin degradation prevention in brain cells.	DMT HRM	4.5 1.5	Katchborian-Neto *et al*. (2020)

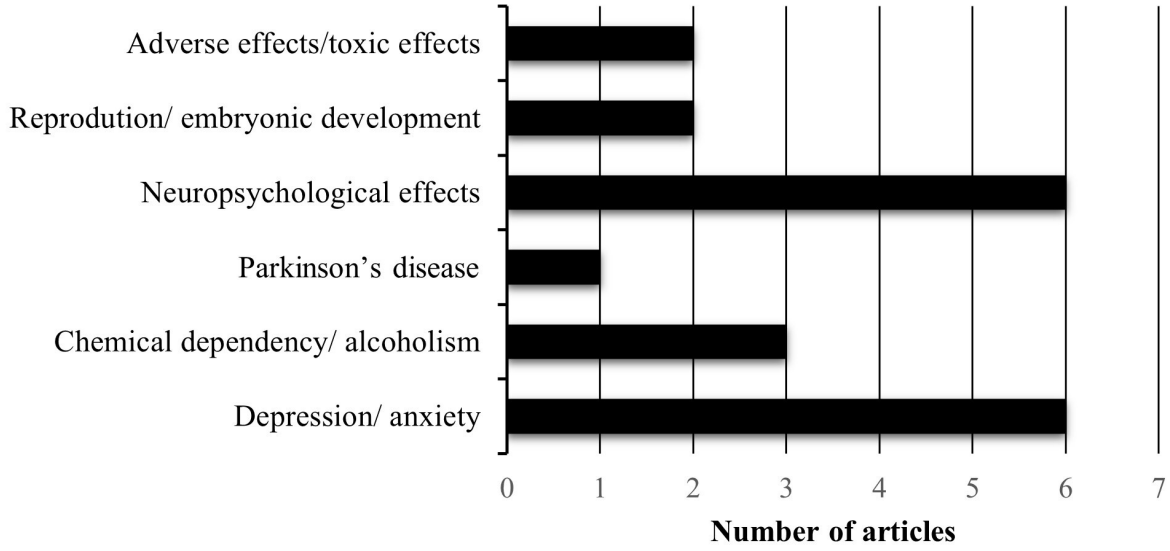


Figure 3. Clinical fields addressed in 20 articles on the therapeutic use of ayahuasca published from 2012 to 2022. The number of articles per field adds up to more than 20 because some articles address more than one field.

DEPRESSION AND ANXIETY

Since the 1980's, depression and anxiety have been the most promising areas with indications for the use of psychedelic drugs, and is still one of the research areas where the evidence is more robust (Dos Santos and Hallak 2020). An open study on the use of ayahuasca was carried out in a psychiatric inpatient unity of the Faculty of Medicine of Ribeirão Preto, São Paulo University (FMRP-USP), in collaboration with the Rio Grande do Norte Federal University (UFRN), with 17 patients diagnosed with recurrent depression (Sanches *et al*. 2016). Each patient received a single dose of 120 to 200 mL of ayahuasca, after which a significant reduction in the scores of the Hamilton depression rating scale (HAM-D), Montgomery-Asberg depression scale (MADRS) and brief psychiatric rating scale (BPRS) was observed, in addition to an increase in the clinician administered dissociative states scale (CADSS). These results suggest a psychoactive effect of ayahuasca and an increase in brain blood perfusion leading to the activation of the accumbens nucleus, insula and subgenuum areas, which are hypoactive cerebral areas in depression.

In a randomized, double-blind, placebo-controlled study by Palhano-Fontes *et al*. (2019), a single dose of ayahuasca was administered to 29 patients with treatment-resistant depression. A significant increse in response rates of disease severity was observed, and the changes remained for seven days after ayahuasca ingestion according to the HAM-D and MADRS scales. A high placebo effect was attributed to patients with low socioeconomic status. Fast effects were observed in individuals with personality disorders, due to the presence of IMAO and DMT, which activate sigma-1 receptors responsible for regulating the brain-derived neurotrophic factor (BDNF) and the nerve growth factor (NGF), two proteins whose regulation and expression seem to be involved in depression pathophysiology.

A study based on an animal model tested the effect of a single dose of 1.67 mL ayahuasca per 300 g body weight in young marmosets (five males and four females) (Silva *et al*. 2019). The results showed significant changes in behavior expression of the animals, more specifically in males, such as an increase in the feeding rate. Serotonin potentially acts as an anorectic agent and the elevation of cortisol levels through ayahuasca is an important orexigenic factor which induces hyperphagia, in addition to the regulation of hormonal response, neural response and the immune system to challenging situations. Thus, the regulation of cortisol was beneficial because depression produces the loss of appetite and body weight.

In another randomized, double-blind, placebo-controlled study carried out in a psychiatric inpatient unit of a hospital, a single oral dose of ayahuasca of 1 mL kg^{-1} body weight was administered to 73 volunteers (28 patients with major depressive disorder [MDD] and 45 patients in the control or placebo group) (Galvão-Coelho *et al*. 2020). The MDD group showed higher levels of reactive C-protein (PCR) in the pre-treatment phase and after the treatment there was a decrease of these levels, in addition to an improvement in depressive symptoms compared to the placebo group. The chronic stress associated with MDD disturbs the balance between the proinflammatory and anti-inflammatory pathways, however, no changes occurred in interleukin 6 (IL-6), BDNF and cortisol levels due to study limitations.

In an open clinical trial carried out in a psychiatric inpatient unit, six volunteers, showed a significant reduction in depressive scores regardless of the current depressive episode after ingestion of 120-200 mL of ayahuasca, as measured on the HAM-D, MADRS and BPRS scales (Osório *et al*. 2015). These effects were attributed to the presence in the ayahuasca decoction of β-carbolines, which are potent MAO inhibitors, and tetrahydroharmine (THH), which acts as an inhibitor of selective serotonin reuptake (ISSR), which can result in elevated levels of brain serotonin and other monoamines.

In 2017-2022 the Global Ayahuasca Project (GAP) was carried out, involving 11,912 participants from all over the world who have had some experience with ayahuasca use (Sarris *et al*. 2021). The GAP adopted a multidisciplinary approach in order to inform the drug and health policies related to the consumption and regulation of ayahuasca. One of the main outcomes explored was the ayahuasca use for the improvement of depression and anxiety, which was the most frequently mentioned effect of ayahuasca ingestion, with 90% of respondents reporting an improvement in symptoms and only a small proportion reporting a worsening of the symptoms.

Overall, the evidence of these observational, preclinical and clinical studies suggests that the use of ayahuasca is generally safe and has potential antidepressant and anxiolytic effects.

CHEMICAL DEPENDENCE AND ALCOHOLISM

Another promising area of investigation and frequently described effect of ayahuasca use is related to the apparent recovery of drug abuse, specially alcohol, tobacco, psychostimulants, *Cannabis* and opiates (Grob *et al*. 1996; Nunes *et al*. 2016). For example, a qualitative ethnographic study based on the experience of individuals recovering from substance dependence through a ritual with ayahuasca use indicated that the healing process combined symbolic and collective dimensions, as ayahuasca promoted a better understanding of "the self", enabling the participants to be more open to a change in behavior, making ayahuasca an option for the understanding to cure the evils that affect the mind (Talin and Sanabria 2017). Pharmacologically, it is believed that so called anti-addictive properties of ayahuasca are related to its action on mesolimbic dopaminergic and serotonergic pathways (Silva *et al*. 2020). Studies like that of Talin and Sanabria (2017) suggest that ayahuasca increases neuroplasticity, facilitates adaptive neural architectural changes and breaks down pathological associations, triggers and cues associated with addiction, since it increases 5-HT levels, attenuating abstinence symptoms (Jacob and Presti 2005). DMT, one of the active components of ayahuasca, is also believed to exert anxiolytic effects through 5-HT_{1A} receptor agonism (Jacob and Presti 2005; Talin and Sanabria 2017).

With regard to alcoholism, a study with male mice models evaluated the effects of ayahuasca on ethanol ingestion (Oliveira-Lima *et al*. 2015). Ayahuasca and ethanol were diluted in 0.9% saline solution and administered intraperitoneally at 10 ml kg^{-1} body weight. All tested ayahuasca doses significantly attenuated the development of ethanol-induced behavioral sensitivity, without affecting the spontaneous locomotor activity, which suggests that the 5HT2-A receptor agonist provoked by ayahuasca components inhibited hyperlocomotion and behavioral sensitivity.

In another study using mice model, ayahuasca was administered by gavage at a dose of 1.76 mg kg^{-1} of DMT based on that used in clinical trials on its effect on depression, anxiety and panic syndrome (Almeida *et al*. 2022). Oral administration of ayahuasca for eight consecutive days was effective in attenuating the expression of ethanol-induced behavioral sensitivity in mice. An anxiolytic effect was observed during ethanol withdrawal and it prevented the ethanol-induced changes in the 5-HT_{1A} receptor and in prodynorphin levels in the hippocampus, while it also reduced the effects of ethanol on dynorphin/prodynorphin in the striatum.

In the surveyed period, we did not find any publication on controlled trials that evaluated the effect of ayahuasca on chemical dependence, despite the positive results of preclinical and observational studies. Thus, it is necessary to carry out controlled trials to better explore that potential.

NEUROPSYCHOLOGICAL EFFECTS

Reports on the neurophysiological experience with the ingestion of ayahuasca are variable, such as visions, mental clarity, sense of life purpose, unconscious manifestations, etc. Several hypotheses have been proposed to explain these effects of ayahuasca, however, in general, they lack scientific testing (Mabit *et al*. 2001; Halpern *et al*. 2008; Shanon *et al*. 2010; Estrela-Parra *et al*. 2019).

In an *in vivo* study on the acute toxicity of ayahuasca, the decoction was administered by gavage to female Wistar rats at 30 and 50 times the dose taken during a religious ritual (Santos *et al*. 2017), followed by 14-day observation. The results showed that ayahuasca influenced the neural systems involved in interoception and emotional processing, as treated animals showed higher neuronal activation in all brain areas involved in serotoninergic neurotransmission (Pic-Taylor *et al*. (2015). Although this led to some brain injury, no permanent damage was detected, suggesting that ayahuasca has antidepressant properties in Wistar rat female at high doses, an effect that should be further investigated (Pic-Taylor *et al*. 2015).

In a clinical trial by Bouso *et al*. (2013), 24 ayahuasca users (11 recurring and 13 occasional users) were evaluated before and after the ingestion of a single oral dose of 100 ml of ayahuasca using a word and color test (Stroop color and word test), a test to measure the verbal work memory (Sternberg working memory task), and a test that measures the components of executive functions (Tower of London task). The results showed mixed effects in neuropsychological performance, as the Stroop test showed improvements, while the Sternberg and Tower of London tests showed harmful effects in occasional users. This suggests that recurring users develop mechanisms to compensate for harmful effects on the executive function, potentially developing a better adaptability to new configurations of tasks or problems.

Changes in serotonin metabolism after ayahuasca consumption result in MAO inhibition, which implies the accumulation of serotonin in nerve terminals leading to serotonergic syndrome (Callaway *et al.* 1999; Gable 2007). This inhibition is positively correlated with most subjective effects of ayahuasca. On the other hand, DMT is considered to be a 5-HT_{2A} receptor agonist (Riga *et al*. 2018), so that the activation of these receptors can modulate 2-arachidonoylglycerol (2-AG) levels (Parrish and Nichols 2006), although its impact at 2-AG peripheral levels is not known. These might be direct mechanisms that support the endocannabinoid modulation by ayahuasca, although it is plausible that more complex mechanisms were involved in the modulation. Furthermore, Madrid-Gambin *et al.* (2022) showed that ayahuasca increased significantly the levels of some corticosteroids, which may be an alternative binding mechanism of ayahuasca to endocannabinoids.

Overall, the available studies suggest a positive effect of ayahuasca regarding the improvement of neuropsychological functions.

NEURODEGENERATIVE DISEASES

Ayahuasca had a therapeutic value for Parkinson's disease in humans. The cytotoxicity of ayahuasca crude extracts and fractions of *B. caapi* and *P. viridis*, as well as the neuroprotection promoted by these samples in a 6-hydroxydopamine (6-OHDA)-induced neurodegeneration model, may be due to the presence of β-carbolines (HRM e HRL) in *B. caapi* vines which act as reversible inhibitors of MAO-A, and this inhibition increases dopamine release by brain cells (Katchborian-Neto *et al*. 2020). In addition to providing protection against neurodegeneration (Serrano-Dueñas *et al*. 2001), the majority of β-carbolines has additional selective serotonin reuptake inhibitor (SSRI) activity (Passos *et al*. 2014; Antonio *et al*. 2019), and are already used for the treatment and made available by the the Brazilian federal public health systemy (SUS in its acronym in Portugues).

Historical assays and preclinical and clinical trials suggest that the *B. caapi* extract is a potentially fast-acting antiparkinsonian agent (Serrano-Dueñas *et al*. 2001; Wang *et al*. 2010; Fisher *et al*. 2018). Controlled trials testing the effect of other isolated components of ayahuasca are needed in order to understand the mechanisms of action interaction among components of the decoction.

OTHER POTENTIAL THERAPEUTIC USES

An open study evaluated the effect of ayahuasca on the suicidal tendency of 17 subjects in a psychiatric inpatient unit (Zeifman *et al*. (2020). Each patient received a single dose of ayahuasca of 2.2 ml kg^{-1} body weight. After ingestion, there was a significant reduction in suicidal tendency according to the MADRS-S scale, and these acute reductions were sustained for 21 days, in addition to a long-term reduction in hopelessness and an increase in experiential acceptance, which reduces the experiential avoidance associated with suicidal tendency. In another study, after follow-up evaluations of 50 eligible subjects in a retreat, the ingestion of ayahuasca showed a significant decrease in grief symptoms, which was maintained over one year of follow-up, in addition to an improvement in the subjects' psychosocial well-being (Gonzalez *et al*. 2020).

In an observational study in a naturalistic environment with 30 long-term participants of ayahuasca retreats carried out in the Netherlands, Spain and Germany designed to assess whether mental health changes were produced by ayahuasca or by set and setting, 14 participants consumed ayahuasca and 16 received a placebo (Uthaug *et al*. 2021). The results suggested that ayahuasca increased emotional empathy to negative stimuli, however the comparison with the placebo

group was not statistically significant, probably due to that the administered therapeutic dose of DMT was lower than the dose administered in clinical settings (Palhano-Fontes *et al*. 2019; Dos Santos *et al*. 2011), which limited the psychedelic experience, in addition to the fact that the participants were aware of the placebo.

SAFETY AND TOXICITY OF AYAHUASCA

The toxicity of ayahuasca in humans is a controversial topic. Among the physical effects reported in the studies included in this review, the most common were vomiting and nausea (reported at least once by over 90% of overall participants in studies with humans), in addition effects such as diarrhea, chills, tremor and tinnitus, which occurred frequently, but were mostly mild and well tolerated. Nausea and vomiting are traditionally not considered to be negative side effects of ayahuasca, as it is part of the ritualistic process where purgation is important (Palhano-Fontes *et al*. 2019; Zeifman *et al*. 2020; Durante *et al*. 2021). The clinical trial by Sanches *et al*. (2016) indicated that ayahuasca is well tolerated by volunteers, as there was no significant increase in blood pressure, heart rate or any other cardiovascular indicator, and no dysphoric effect was reported.

Many conventional drugs cause some degree of MAO inhibition, an effect explored in antidepressants (Durante *et al*. 2021). The inhibition of MAO results in the accumulation of substances that otherwise tend to degrade, including endogenous neurotransmitters. If the inhibition of MAO is too intense or prolonged, the increase of monoamine concentration can result in systemic manifestations (Yamada and Yasuhara 2004). When combined with monoaminergic substances, some IMAO can cause deleterious reactions (McCabe-Sellers *et al*. 2006; Volpi-Abadie *et al*. 2013). A worrying result of inhibiting MAO enzymes, specially in combination with serotonergic agents, is the accumulation of serotonin to toxic levels, a condition known as "serotonergic syndrome", which, although rare, can be fatal (Volpi-Abadie *et al*. 2013).

Ayahuasca was toxic for pregnant rats, resulting in mortality of 42% and 58% of treated females (at the two highest doses), and inducing discernible histopathological changes in the kidneys (hydropic cell degeneration) of nearly half the rats that survived to euthanasia, as well as a significant decrease in the number of viable neurons in the hippocampus and brain regions of the rats that survived the highest dose, which probably led to a disruption of the neuronal layer (Motta *et al*. 2018). The 2-times dose resulted in decreased viable neurons in the CA1 hippocampal layer, but the lowest dose tested (1-time, the human dose, corresponding to 343 mg kg^{-1} bw day^{-1}) caused only a small increase in the incidence of skeleton and soft-tissue variations (considered to be of minor toxicological significance) it was determined as the study NOAEL (non-observed-adverse-effect-level) for developmental toxicity.

Santos *et al*. (2017) investigated the reproductive effects of ayahuasca on male Wistar rats after chronic exposure. The rats were treated by gavage every other day for 70 days at 0 (control), 1, 2, 4 and 8 times the dose used in a religious ritual. No significant changes were found in the reproductive endpoints (spermatozoid motility and morphology, total spermatozoid count and daily sperm production), and histology of testis and epididymis, there was higher neuronal activity in brain areas rich in serotonergic receptors, such as the amygdala, the raphe nucleus and the hippocampus.

As in the study by Pic-Taylor *et al*. (2015), the actual lethal oral dose for Wistar rats could not be determined, but was shown to be higher than 50 times the ritual dose (15.1 mg kg^{-1} DMT).

Ayahuasca effects on zebrafish, *Danio rerio* Hamilton (Cyprinidae) embryo development and neurobehavior were first reported by Andrade *et al*. (2018). The embryos were exposed to different concentrations of ayahuasca (0; 0.064; 0.3; 1.6; 8; 40; 200 and 1000 mg L^{-1} of the lyophilized material diluted in zebrafish culture water) for 96 hours. Embryos were observed daily and the following parameters evaluated: mortality, incidence of pericardial edema and red blood cell accumulation, malformations, hatching, equilibrium and developmental delay. Mortality occurred at the highest administered dose with an acute toxicity of 236.3 mg L^{-1}. After exposure to ayahuasca, the embryos showed developmental anomalies, such as loss of balance, reduced locomotor activity and edema. The authors suggest an excessive serotonergic stimulation caused by DMT, which can cause cardiovascular collapse and reduce the hatching rate. Similarly, rats exposed to daily doses of ayahuasca (more than double the ritual dose) (Santos *et al*. 2017)) during pregnancy showed reduced reproduction rates, lower body weight and lower relative weight of fetal organs and visceral malformations (Mota *et al*. 2013).

The toxicity studies reported in this review do not provide solid and conclusive information regarding the safety of using ayahuasca and its active components. Therefore, more studies are needed to define the toxicological classification parameters in accordance with government regulatory agencies.

CONCLUSIONS

Evidence from the studies included in this review suggests that ayahuasca, as a pharmacological agent, can produce beneficial effects on mood, mental health and Parkinson's disease. The data from controlled clinical trials corroborate the traditional use for antidepressant and anxiolytic effects in drug and alcohol dependence. However, these effects need to be investigated in controlled trials with larger samples. Although ayahuasca has therapeutic potential, studies with greater methodological rigor are required to clarify the action mechanisms of ayahuasca in detail, and to evaluate its toxicity

potential more thoroughly, to clinically establishing its safety thresholds for pharmacological use.

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REFERENCES

Almeida, C.A.F.; Junior, A.A.P.; Rangel, J.G.; Pereira, B.P.; Costa, K.C.M.; Bruno, V.; et al. 2022. Ayahuasca, a psychedelic beverage, modulates neuroplasticity induced by ethanol in mice. *Behavioural Brain Research*, 416: 113546.

Andrade, T.S.; Oliveira, R.; Silva, L.M.; Zuben, M.V.V.; Grisolia, C.K.; Domingues, I.; Caldas, E.D. et al. 2018. Exposure to ayahuasca induces developmental and behavioral alterations on early life stages of zebrafish. *Chemico-Biological Interactions* 293: 133-140.

Antonio, E.; Parra, E.; Cesar, J.; Pérez, A.; Javier, F.; Aguilar, A. 2019. Ayahuasca: uses, phytochemical and biological activities. *Natutal Products Bioprospect* 9: 251–265.

Bezerra, M.L. 2020. Efeito da disponibilidade de recursos do ambiente na variabilidade intraespecífica do cipó *Banisteriopsis caapi.* Master's dissertation, Instituto Nacional de Pesquisas da Amazônia (INPA), Brasil, 75p. (https://repositorio.inpa.gov.br/handle/1/36422).

Bouso, J.C.; Fábregas, J.M.; Antonijoan, R.M.; Fornells, A.; Riba, J. 2013. Acute effects of ayahuasca on neuropsychological performance: differences in executive function between experienced and occasional users. *Psychopharmacology* 3: 415-424.

Brito-da-Costa, A.; Dias-da-Silva, D.; Gomes, N.; Dinis-Oliveira, R.; Madureura-Carvalho, R. 2020. Toxicokinetics and toxicodynamics of ayahuasca alkaloids N,N-dimethyltryptamine (DMT), harmine, harmaline and tetrahydroharmine: Clinical and forensic impact. *Pharmaceuticals* 13: 334. doi.org/10.3390/ph13110334.

Callaway, J.C.; McKenna, D.J.; Grob, C.S.; Brito, G.S.; Raymon, L.P.; Poland, R.E.; Andrade, E.N.; Andrade, E.O.; Mash, D.C. 1999. Pharmacokinetics of hoasca alkaloids in healthy humans. *Journal of. Ethnopharmacology* 3: 243–256.

Costa, M.C.M.; Figueiredo, M.C.; Cazenave, S.D.O.S. 2005. Ayahuasca: uma abordagem toxicológica do uso ritualístico. *Archives of Clinical Psychiatry* 32: 310-318.

Daldegan-Bueno, D.; Simionato, N.M.; Favaro, V.M.; Maia, L.O. 2022. The current state of ayahuasca research in animal models: A systematic review. *Progress in Neuropsychopharmacology & Biological Psychiatry* 125: 110738.

Dos Santos, R.G.; Hallak, J.E.C. 2020. Therapeutic use of serotoninergic hallucinogens: A review of the evidence and of the biological and psychological mechanisms. *Neuroscience and Biobehavioral Reviews* 108: 423-434.

Durante, I.; Santos, R.G.; Bouso, J.C.; Hallak, J.E. 2021. Risk assessment of ayahuasca use in a religious context: self-reported risk factors and adverse effects. *Brazilian Journal of Psychiatry* 43: 362-369.

Estrela-Parra, E.A.; Almanza-Pérez, J.C.; Alarcón-Aguilar, F.J. 2019. Ayahuasca: Uses, phytochemical and biological activities. *Natural Products and Bioprospecting* 9: 251–265.

Fisher, R.; Lincoln, L.; Jackson, M.J.; Abbate, V.; Jenner, P.; Hider, R.; et al. 2018. O efeito de *Banisteriopsis caapi (B. caapi)* sobre os déficits motores no modelo de sagui comum tratado com MPTP da doença de Parkinson. *Pesquisa em Fitoterapia* 32: 678-687.

Gable, R.S. 2007. Risk assessment of ritual use of oral dimethyltryptamine (DMT) and harmala alkaloids. *Addiction* 1: 24–34.

Galvão-Coelho, N.L.; Galvão, A.C.M.; Almeida, R.N.; Fontes, F.; Braga, I.C.; Soares, B.L.; et al. 2020. Changes in inflammatory biomarkers are related to the antidepressant effects of Ayahuasca. *Journal of Psychopharmacology* 34: 1125-1133.

Garrido, D.; Sousa, M.; Ona, G.; Santos, R.G.; Hallak, J.E.C.; Córcoles, M.A.A.; Bouso, J.C. 2020. Effects of ayahuasca on mental health and quality of life innaïve users: A longitudinal and cross-sectional study combination. *Scientific Reports* 10: 1-12. doi.org/10.1038/s41598-020-61169-x

Gonçalves, J.; Luís, Â.; Gallardo, E.; Duarte, A.P. 2023. A systematic review on the therapeutic effects of ayahuasca. *Plants* 12: 13-2573.

González, D.; Cantillo, J.; Pérez, I.; Farré, M.; Feilding, A.; Obiols, J.E.; et al. 2020. Therapeutic potential of ayahuasca in grief: a prospective, observational study. *Psychopharmacology* 4: 1171-1182.

Grob, C.S.; Danforth, A.L.; Chopra, G.S.; Hagerty, M.; Mckay, C.R.; Halberstadt, A.L.; et al. 2011. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Archives of General Psychiatry* 1: 71–78.

Halpern, J.H.; Sherwood, A.R.; Passie T.; Blackwell K.C.; Ruttenber A.J. 2008. Evidence of health and safety in American members of a religion who use a hallucinogenic sacrament. *Medical Science Monitor* 8: SR15-22.

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* 2: 108-128.

Hanks, J.B.; González-Maeso, J. 2013. Animal models of serotonergic psychedelics. *ACS Chemical Neuroscience* 4: 33-42.

Jacob, M.S.; Presti, D.E. 2005. Endogenous psychoactive tryptamines reconsidered: An anxiolytic role for dimethyltryptamine. *Medical Hypotheses* 5: 930-937.

Jaster, A.M.; Revenga, M.F.; González-Maeso, J. 2022 Molecular targets of psychedelic-induced plasticity. *Journal of Neurochemistry* 162: 80-88.

Kaasik, H.; Souza, R.C.Z.; Zandonadi, F.S.; Tófoli, L.F.A.; Sussulini, A. 2021. Chemical composition of traditional and analog ayahuasca. *Journal of Psychoactive Drugs* 53: 65-75.

Katchborian-Neto, A.; Santos, W.T.; Nicácio, K.J.; Corrêa, J.O.A.; Murgu, M.; Martins, T.M.M.; et al. 2020. Neuroprotective potential of Ayahuasca and untargeted metabolomics analyses: applicability to Parkinson's disease. *Journal of Ethnopharmacology* 225: 1-16. doi.org/10.1016/j.jep.2020.112743

Keiser, M.J.; Setola, V.; Irwin, J.J.; Laggner, C.; Abbas, A.I.; Hufeisen, S.J.; et al. 2009. Predicting new molecular targets for known drugs. *Nature* 462: 175–181.

Labate, B.C.; MacRae, E. 2016. *Ayahuasca, Ritual and Religion in Brazil*. 1st ed. Taylor and Francis, Boca Raton, 256p.

Mabit, J. 2001. Blending traditions - Using indigenous medicinal knowledge to treat drug addiction. *Psychotropes: Revue Internationale des Toxicomanies* 7: 7-18.

Madrid-Gambin, F.; Gomez-Gomez, A.; Busquets-Garcia, A.; Haro, N.; Marco, S.; Mason, N. L.; et al. 2022. Metabolomics and integrated network analysis reveal roles of endocannabinoids and large neutral amino acid balance in the ayahuasca experience. *Biomedicine & Pharmacotherapy* 149: 112-845.

McCabe-Sellers, B.J.; Staggs, C.G.; Bogle, M.L. 2006. Tyramine in foods and monoamine oxidase inhibitor drugs: a crossroad where medicine, nutrition, pharmacy, and food industry converge. *Journal of Food Composition and Analysis* 19: S58-S65.

Mota, L.S.G. 2013. *Toxicidade aguda, neurotoxicidade, toxicidade reprodutiva e embriotoxicidade do chá ayahuasca (Banisteriopsis caapi e Psychotria viridis) em ratas Wistar*. Master's dissertation, Universidade de Brasília – UnB, Brazil, 82p. (http://repositorio.unb.br/handle/10482/15291).

Motta, L.G.; Morais, J.A.; Tavares, A.C.A.; Vianna, L.M.S.; Mortari, M.R.; Amorim, R. F.B.; et al 2018. Maternal and developmental toxicity of the hallucinogenic plant-based beverage ayahuasca in rats. *Reproductive Toxicology* 77: 143-153.

Nunes, A.A.; Santos, R.G.; Osório, F.L.; Sanches, R.F.; Crippa, J.A.; Hallak, J.E. 2016. Effects of ayahuasca and its alkaloids on drug dependence: a systematic literature review of quantitative studies in animals and humans. *Journal of Psychoactive Drugs* 48: 195-205.

Oliveira-Lima, A.J.; Santos, R.; Hollais, A.W.; Gerardi-Junior, C.A.; Baldaia, M.A.; Wuo-Silva, R.; et al. 2015. Effects of ayahuasca on the development of ethanol-induced behavioral sensitization and on a post-sensitization treatment in mice. *Physiology & Behavior* 142: 28-36.

Orsolini, L.; Chiappini, S.; Papanti, D.; Latini, R.; Volpe, U.; Fornaro, M.; et al. 2020. How does ayahuasca work from a psychiatric perspective? Pros and cons of the entheogenic therapy. *Human Psychopharmacology: Clinical and Experimental* 3: e2728.

Osório, F.L.; Sanches, R.F.; Macedo, L.R.; Santos, R.G.; Maia-Oliveira, J.P.; Wichert-Ana, L.; et al. 2015. Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report. *Brazilian Journal of Psychiatry* 37: 13-20.

Palhano-Fontes, F.; Barreto, D.; Onias, H.; Andrade, K.C.; Novaes, M.M.; Pessoa, J.A.; et al. 2019. Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. *Psychological Medicine* 49: 655-663.

Parrish, J.C.; Nichols, D.E. 2006. Serotonin 5-HT(2A) receptor activation induces 2- arachidonoylglycerol release through a phospholipase c-dependent mechanism. *Journal of Neurochemistry* 4: 1164–1175.

Passos, C.D.S.; Simoes-Pires, C.; Henriques, A.; Cuendet, M.; Carrupt, P.; Christen, P.; 2014. Alkaloids as inhibitors of monoamine oxidases and their role in the central nervous system. *Studies in Natural Products Chemistry* 43: 123–144.

Pic-Taylor, A.; Motta, L.G.; Morais, J.A.; Júnior, W.M.; Santos, A.D.F.A.; Campos, L.A.; et al. 2015. Behavioural and neurotoxic effects of ayahuasca infusion (*Banisteriopsis caapi* and *Psychotria viridis*) in female Wistar rats. *Behavioural Processes* 118: 102-110.

Ramos, E.M. 2021. Avaliação do potencial farmacológico do chá de ayahuasca no manejo da ansiedade e depressão. *Saúde e Desenvolvimento Humano* 1: 1-9. dx.doi.org/10.18316/sdh.v10i1.8006

Riga, M.S.; Llad´o-Pelfort, L.; Artigas, F.; Celada, P. 2018. The serotonin hallucinogen 5-MeO-DMT alters cortico-thalamic activity in freely moving mice: Regionally selective involvement of 5-HT 1A and 5-HT 2A receptors. *Neuropharmacology* 142: 219–230.

Sanches, R.F.; Osório, F.L.; Santos, RG.; Macedo, L.R.H.; Maia-De-Oliveira, J.P.; Wichert-Ana, L.; et al. 2016. Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: A SPECT study. *Journal of Clinical Psychopharmacology* 36: 77-81.

Santos, A.D.F.A.; Vieira, A.L.S.; Taylor, A.; Caldas, E.D. 2017. Reproductive effects of the psychoactive beverage ayahuasca in male Wistar rats after chronic exposure. *Revista Brasileira de Farmacognosia* 27: 353-360.

Sarris, J.; Perkins, D.; Cribb, L.; Schubert, V.; Opaleye, E.; Bouso, J.C.; 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.

Schripsema, J.; Dagnino, D. 2017. Alcaloides indólicos. In: Simões, C.M.O.; Schenkel, E.P.; De Mello, J.P.C.; Mentz, L.A.; Petrovick, P.R. (Eds.). *Farmacognosia: Do Produto Natural ao Medicamento*. Artmed, Porto Alegre. p.368-387.

Serrano-Dueñas, M.; Cardozo-Pelaez, F.; Sánchez-Ramos, J. 2001. Efeitos do extrato de *Banisteriopsis caapi* na doença de Parkinson. *Scientific Review of Alternative Medicine* 5: 129-134.

Shanon, B. 2010. The epistemics of ayahuasca visions. *Phenomenology and the Cognitive Sciences* 9: 263-280.

Silva, F.S.; Silva, E.A.; Souza, G.M.D.; Maia-De-Oliveira, J.P.; Soares-Rachetti, V.P.; Araujo, D.B.; et al. 2019. Acute effects of ayahuasca in a juvenile non-human primate model of depression. *Brazilian Journal of Psychiatry* 4: 280-288.

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.

Thevenin, J.M.R. 2017. *Natureza nos Caminhos da Ayahuasca: territorialidade, arranjos institucionais e aspectos fitogeográficos de conservação florestal na Amazônia (Rondônia/Brasil).* Doctoral thesis, Universidade Estadual Paulista (UNESP), Brazil, 189p. (http://hdl.handle.net/11449/150410).

Uthaug, M.V.; Mason, N.L.; Toennes, S.W.; Reckweg, J.T.; Sousa Fernandes Perna, E.B.; Kuypers, K.P.C.; et al. 2021. Placebo-controlled study of the effects of ayahuasca, set and setting on mental health of participants in ayahuasca group retreats. *Psychopharmacology* 238: 1899-1910.

Volpi-Abadie, J.; Kaye, A.M.; Kaye, A.D. 2013. Serotonin syndrome. *Ochsner Journal* 13: 533-540.

Wang, Y.H.; Samoylenko, V.; Tekwani, B.L.; Khan, I.A.; Miller, L.S.; Chaurasiya, N.D.; et al. 2010. Composition, standardization and chemical profiling of *Banisteriopsis caapi*, a plant for the treatment of neurodegenerative disorders relevant to Parkinson's disease. *Journal of Ethnopharmacology* 3: 662-671.

Yamada, M.; Yasuhara, H. 2004. Clinical pharmacology of MAO inhibitors: safety and future. *Neurotoxicology* 25: 215-21.

Zeifman, R.J.; Singhal, N.; Santos, R.G.; Sanches, R.F.; Osório, F.L.; Hallak, J.E.; et al. 2020. Rapid and sustained decreases in suicidality following a single dose of ayahuasca among individuals with recurrent major depressive disorder: results from an open-label trial. *Psychopharmacology* 238: 453-459.

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