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Ayahuasca

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1. What is ayahuasca?

Ayahuasca is the Quechua word referring to a liquid produced by the slow decoction or admixture of the Amazonian *Banisteriopsis caapi* vine – as well as to the vine itself – which contains harmine, harmaline and tetrahydroharmine. It is traditionally used throughout the Northwestern Amazon, originating from indigenous cultures that have used it for hundreds of years for medicinal and ritual purposes. At the beginning of the last century, syncretic religions incorporating shamanic worldviews into Christian rituals began to use ayahuasca. In the early 20th century, these churches expanded into Amazonian urban centers (Labate, 2004) and, over the last thirty years, globally (Labate & Jungaberle, 2011).

Based on the intended use of the decoction or admixture of the vine called ayahuasca, each Amazonian culture, shaman, healer, man or woman with experience using ayahuasca, adds different plants to the brew with the objective of searching for a specific effect depending on the disease to be healed or ritual to be performed. Ethnographic studies suggest that there are more than 5,000 different ways to prepare ayahuasca, all using *B. caapi* as their base (Fericgla, 1997). Some of these traditional recipes, considering both the indigenous cultures and the religions that use ayahuasca as their sacrament (or "ayahuasca religions"), include adding leaves of the *Psychotria viridis* bush, which contains DMT (*N,N*-Dimethyltryptamine), along with the *B. caapi* vine (Schultes & Hofmann, 1992). Ayahuasca is currently being popularized as the combination of *B. caapi* and *P. viridis*, likely because the international expansion of ayahuasca practices was initiated by these churches (Sánchez & Bouso, 2015).

The precise historical beginning of ayahuasca use is unknown. Archaeological evidence has dated the use of ayahuasca to more than 1,000 years (Miller et al., 2019). Among Amazonian ethnic groups, the use of ayahuasca decoctions/admixtures that also contain plants with DMT seems to be a more recent phenomenon (Brabec de Mori, 2011).

Ayahuasca is considered a sacred drink by innumerable indigenous Amazonian groups and a medicine by mestizo healers in much of South America. The traditional and modern use of ayahuasca extends from Panama to Bolivia, including Peru, Ecuador, Colombia, and Brazil – countries in which its medicinal use is deeply present in urban centers (Luna, 1986, 2011). A pioneering 1986 work that brought together all the scientific information on ayahuasca available at that time found more than 400 bibliographical references on the ethnography of ayahuasca (Luna, 1986b), references to more than 70 different Amazonian ethnic groups where it was used traditionally, and more than 40 vernacular names given to the decoction (Luna, 1986c). Ayahuasca is currently being used as a medicine in ceremonies officiated by indigenous peoples, mestizos, and diverse professionals who have learned to use it in its places of traditional origin (Labate & Bouso, 2013; Labate & Cavnar, 2014a; Labate, Cavnar & Gearin, 2017; Labate et al., 2009; Luna, 2011).

2. The legal status of ayahuasca

As noted above, ayahuasca is typically produced by the slow decoction/admixture of two plants – *B. caapi* and *P. viridis*. The latter of these two plants contains DMT (*N,N*-dimethyltryptamine), a tryptamine alkaloid listed in the 1971 Convention on Psychotropic Substances, and many countries therefore also include it in their national legislation. Although DMT is listed in Schedule I of the 1971 Convention (the most restrictive category), the International Narcotics Control Board

(INCB), a quasi-judicial control body for the implementation of the United Nations drug conventions, has stated on several occasions that ayahuasca – as well as other psychoactive plants – is not subject to international control.

In its 2010 Annual Report, the INCB stated that "although some active stimulant or hallucinogenic ingredients contained in certain plants are controlled under the 1971 Convention, no plants are currently controlled under that Convention or under the 1988 Convention. Preparations[1] (e.g. decoctions for oral use) made from plants containing those active ingredients are also not under international control" (paragraph 284, INCB, 2010).

The alkaloids present in the *B. caapi* vine are also not subject to international control. In 2008, ayahuasca was declared Cultural Patrimony of Peru, due to its ancestral use as a traditional medicine (Instituto Nacional de Cultura, 2008) and its use for religious purposes is firmly established and legalized in Brazil (Labate et al., 2009). The religious use of ayahuasca has been permitted for some churches in the USA and Canada, and the churches in which ayahuasca is considered a sacrament and is consumed for that purpose have expanded internationally into numerous European, American, and Asian countries (Labate et al., 2009; Labate & Feeney, 2012; Sánchez & Bouso, 2015).

3. The pharmacology of ayahuasca

The mechanism of action by which ayahuasca produces its effects is highly sophisticated. The harmala alkaloids (harmine, harmaline and tetrahydroharmine) have the property of acting as inhibitors of monoamine oxidase (MAO), an enzyme present in the gastrointestinal tract that degrades monoamines. As DMT is a monoamine, if it is ingested orally, the endogenous MAO deactivates it, preventing it from reaching the brain. At some point in the remote past, the indigenous people of the Amazon Basin discovered that adding the leaves of *Psychotria viridis* (which, as previously mentioned, contain DMT) to a decoction/admixture of *Banisteriopsis caapi* (which contains harmala alkaloids), makes the DMT bioactive. This is due to the harmala alkaloids, which, acting as MAO inhibitors (MAOIs), block the MAO present in the gastrointestinal tract and in this way the DMT present in the leaves of *P. viridis* can reach the brain (McKenna et al., 1984; Riba et al., 2003). Pure DMT on its own is inactive when consumed orally (Riba et al., 2015). This sophisticated indigenous discovery was only recently rediscovered by science in the 1980s. DMT is found in its natural form in many animal species (Shulgin & Shulgin, 1997) and in human urine, blood, and cerebrospinal fluid (Barker et al., 2012). Its physiological role remains unknown.

During the last few decades, clinical trials have been carried out on humans where both DMT (in purified form, administered intravenously) and ayahuasca (administered orally) have been administered in a laboratory context, and their acute effects have been characterized both at the psychological and somatic levels. In these studies, it has been demonstrated that DMT and ayahuasca have very different pharmaco-dynamics. The acute effects of DMT appear in an intense and almost immediate way after its intravenous administration (Strassman & Qualls, 1994; Strassman et al., 1994), while ayahuasca produces effects in a slower and more progressive way, beginning from 45 to 60 minutes after administration, reaching maximum effects after 2 hours,

[1] The Article 1 from the 1971 Convention, which is dedicated to specify the terms used in the treaty, understands as preparation: "1) Any solution or mixture, in whatever physical state, containing one or more psychotropic substances, or 2) One or more psychotropic substances in dosage form." Therefore, since ayahuasca is a decoction/admixture of plants that are not controlled, and not a mixture of active principles, then the term "preparation," according to the definition of the treaty, is not appropriate when referring to ayahuasca (Art. 1, f) i)).

which disappear after 4 to 6 hours (Riba, 2003; dos Santos, 2011). The maximum intensity of the effects of DMT is approximately two times that of ayahuasca at equivalent doses (Grob et al., 1996), which makes the global effects of ayahuasca much more controllable than pure DMT. In addition, since ayahuasca is a decoction made with plants there are also other compounds (beta-carbolines) that may modulate the effects and thus make them significantly different from pure DMT. In addition, it must be taken into account that, like with other natural preparations, ayahuasca also contains other compounds found in the plant kingdom, such as flavonoids and terpenes. A recent study quantified about 2,000 components in the final ayahuasca brew (Katchborian-Neto et al., 2020).

4. The effects of ayahuasca

Ayahuasca, whether administered in a laboratory context or ingested in a traditional context, producestransitory modifications in emotion, thought content, perception and somatic sensations – as evaluated through questionnaires to measure its subjective effects – while the capacity of the individual to interact with its surroundings is significantly preserved (Grob et al.,1996; Riba et al., 2001, 2003; dos Santos et al., 2011, 2012), even to the point of being able to carry out complex cognitive performance tests (Bouso et al., 2013). The volunteers in these studies also describe the effects of ayahuasca as "well tolerated" (Riba et al., 2001, 2003; dos Santos et al., 2011, 2012). The curve of effects that ayahuasca produces corresponds with the curve of the presence of DMT and harmalines (MAOIs) in plasma, which disappears from the organism after eight hours (Riba et al., 2003; Schenberg et al., 2015).

Studies have been published where neuroimaging techniques were used to determine which cerebral areas are activated after the ingestion of ayahuasca. Two studies showed that ayahuasca activates the cortical and paralimbic areas. Specifically, in the first of these studies (Riba et al., 2006), bilateral increments in cerebral perfusion were found in the inferior frontal gyrus and the anterior insula, the activity being most intense in the right hemisphere. Activations in the anterior cingulate and medial frontal cortex in the right hemisphere, areas involved in awareness of interoceptive and emotional processes, as well as emotional arousal, were also found. Increased cerebral blood flow in the ventral anterior cingulate gyrus and the subcallosal was also recorded, structures that are related to decision-making and emotions. The left amygdala, a structure involved in the processing of potentially threatening stimuli, and the parahippocampal convolution, a structure associated with the hippocampus and intimately involved in the processing of memories, also showed higher blood perfusion compared to placebo. No differences were found compared to placebo in any other area of the brain.

In another second neuroimaging study performed with Functional MRI (fMRI), activation in primary visual areas was also found, and when subjects under the influence of ayahuasca were remembering a photograph its magnitude was comparable to baseline activation levels recorded with the presentation of a natural image with eyes open (de Araujo et al., 2011). According to the authors, this effect causes the brains of volunteers to interpret the ayahuasca experience as if it was "real," not in the sense of a hallucinatory experience, but by the experiential endowment of conscious experience. This overall pattern of activation may be at the base of the introspective processes, memories of past experiences charged with emotional connotations, and complex cognitive processes, which are so prototypical of the ayahuasca experience (Shanon, 2002).

In fact, a recent fMRI study showed a deactivation of a neural network known as the Default Mode Network (DMN) (Palhano-Fontes et al., 2015). This network, which includes different brain

structures, is thought to be involved in internal mental processes, such as the sense of "I," or the mental imagery produced when a person is in a state of relaxation. Abnormal increases in DMN activity were observed in a wide spectrum of neurological disorders such as autism, Parkinson's and Alzheimer's disease, and psychiatric disorders such as schizophrenia and depression (Mohan et al., 2016). In this study, it was observed that ayahuasca decreased DMN activity, a finding also observed with other similar psychoactive substances, such as psilocybin (Carhart-Harris et al., 2012). These effects have also been replicated by researchers who administered DMT on its own and found decreases in alpha and beta waves (Timmermann et al., 2019).

When considered together, these cerebral, cognitive, and emotional phenomena could explain why ayahuasca is considered an ethnobotanical tool with psychotherapeutic potential (Labate & Cavnar, 2013). In fact, one study found that ayahuasca reduced panic and hopelessness scores in experienced users (dos Santos et al., 2007).

5. Long-term effects

Studies of medium- and long-term ayahuasca use have shown evidence of either neuropsychological or psychopathological alterations associated with the continuous use of ayahuasca. One prospective study conducted among people that ingested ayahuasca for the first time showed improvements on mental health measures and physical pain reduction for six months after initiation to ceremonial ayahuasca use (Barbosa et al., 2005, 2009). Other studies have shown better indicators of psychopathology and higher psychosocial wellness among regular ayahuasca users (Bouso et al., 2012; Halpern et al., 2008) and three studies did not find neuropsychological alterations measured with cognitive performance tests among regular users of ayahuasca after years of continuous use (Grob et al., 1996; Barbosa et al., 2016; Bouso et al., 2012; Bouso et al., 2015). One of these studies compared 127 ayahuasca users with a history of ritual ayahuasca use of at least 15 years with 115 controls, and observed better scores on psychopathological measures and in some neuropsychological tests among the ayahuasca users – results that remained consistent in two evaluations separated by one year (Bouso et al., 2012). Studies with adolescent members of a Brazilian UDV church also failed to observe any neuropsychological or psychiatric alterations associated with ritual ayahuasca use (da Silveira et al., 2005; Doering-Silveira et al., 2005b).

Finally, a recent neuroimaging study with Spanish members of the Santo Daime church with participants who had a history of ayahuasca use of at least 50 occasions in the past two years found differences on cortical thickness among the ayahuasca users compared to a control group. Differences in cortical thickness were only correlated with the personality variable "Self-Transcendence," suggesting that ayahuasca may produce brain alterations that could manifest as increased spiritual tendencies (Bouso et al., 2015). Ayahuasca users in this study had similar scores to the control group of non-users on psychopathological tests and on neuropsychological function, showing that the structural changes possibly associated with ayahuasca use did not relate to brain toxicity, but to personality changes that simply reflect a "different," but not pathological, way of being, as has been shown in several previously cited studies (Grob et al., 1996; Barbosa et al., 2009 Barbosa et al., 2016; Bouso et al., 2012; da Silveira et al., 2005; Doering-Silveira et al., 2005b; Halpern et al., 2008). These kinds of brain alterations are also known to be produced through training and practice in numerous activities, such as learning music, and are known as cerebral plasticity – a normal phenomenon that occurs in our brains continuously throughout our lives.

6. Adverse effects and safety

Some adverse effects associated with ayahuasca administration in laboratory contexts have been reported, although these were rare and isolated cases that were resolved without the need for intervention (Riba & Barbanoj, 2005). There are some cases describing psychiatric symptomatology in ritual contexts, although these cases are rare (Lima & Tófoli, 2011; dos Santos & Strassman, 2011) and their occurrence seems to be below the prevalence of psychiatric problems in the general population. In any case, these data suggest that ayahuasca is, in principle, contraindicated for people with grave psychiatric disorders, particularly those individuals prone to psychosis.

Although ayahuasca is psychoactive, this does not mean that the doses that are usually ingested in sessions produce organic or brain toxicity. In this sense, and according to toxicology science, the minimum psychoactive dose should not be equivalent to the toxic dose, if toxicity is considered the capacity of a substance to induce harm to an organism by means of its chemical properties after being in contact with the organism (Baños & Farré, 2002). Regarding the effects of ayahuasca in the organism, studies performed with volunteers both in the laboratory (Riba, 2003; dos Santos, 2011) and in natural contexts (McKenna, 2004) show that ayahuasca is physiologically safe. The impact of ayahuasca on the cardiovascular system is minimal, producing only slight increases in blood pressure and heart rate that have no clinical implications (Riba et al., 2001, 2003; dos Santos et al., 2012). It was also observed that ayahuasca induces transitory increases in the levels of the hormones prolactin, cortisol, and growth hormone (dos Santos et al., 2011, 2012), and with regards to the immune system, ayahuasca time-dependently reduces subpopulations of CD4 and CD3 lymphocytes and increases natural killers (NK) cells (dos Santos et al., 2011, 2012). These transitory physiological effects do not seem to have negative consequences – in studies where general blood analysis were performed in subjects before and after the participation in the trials, no hematological or biochemical alterations were found (Riba et al., 2001; Riba & Barbanoj, 2005). A recent study assessing hepatic function in regular ayahuasca users (twice a month or more for at least one year) failed to find alterations in hepatic markers and function (Mello et al., 2019).

The main adverse effects produced by ayahuasca are nausea and vomiting (Callaway et al., 1999; Riba et al., 2001; Riba, 2003; Riba & Barbanoj, 2005; dos Santos, 2011; dos Santos et al., 2012). The emetic action of ayahuasca is related first to the organoleptic properties of the admixture, and second to its serotonergic action (Callaway et al., 1999). These are not considered important adverse reactions by session participants, where they are understood as potential therapeutic effects and called “la purga” (“the purge”) in traditional Amazonian medicine (Luna, 1986, 2011). In traditional contexts, the “purge” is understood as a physical and psychological cleansing from internal conflicts that may distress the participant and is considered an essential part of the therapeutic benefits (Luna, 1986, 2011). The emetic effects of ayahuasca are, in fact, one of the main reasons why it does not have a potential for recreational use.

Finally, two recently published studies evaluated the adverse effect profile of ayahuasca in naturalistic contexts. In the first article, Durante et al. (2020) authors reported that the most common adverse effects experienced in a sample of 614 people were gastrointestinal symptoms, an effect noted above. However, despite being considered as adverse events from a medical perspective, these effects are actually desired for users, who consider this process as part of a necessary purge. Remarkably, the use of prescription medication or having a history of psychiatric diagnosis were not associated with suffering more adverse events. A higher frequency of physical

adverse effects such as tachycardia, dizziness, or tremors was recorded in the sub-sample (50 people) who had a psychiatric diagnosis (mainly depression and anxiety). The second study, authored by Gómez-Sousa et al. (2021), focused on acute adverse reactions recorded in a ceremonial context by people taking ayahuasca for the first time. In a sample of 40 people, they found a total of seven cases (17.5%); four of the seven subjects met criteria for a psychiatric diagnosis prior to taking ayahuasca. The authors emphasize the fact that even after having suffered acute adverse events, the subjects developed neither psychiatric symptoms nor experienced long-term consequences. In contrast, positive effects were recorded, such as a reduction in criteria for the diagnosis of psychiatric disorders (Gómez-Sousa et al., 2021).

7. The abuse potential of ayahuasca and its anti-addictive properties

Studies with healthy volunteers have also shown that ayahuasca does not produce tolerance (dos Santos et al., 2012), thus it is not necessary to increase the dose to achieve the desired effects, which, together with the emetic effects, protect consumers from overdose.

Regarding the abuse potential of ayahuasca, in the neuroimaging studies with healthy volunteers described above, no activation of brain areas related to the reward systems was observed – the brain areas activated by drugs with potential for abuse. Moreover, the available evidence suggests that ayahuasca could be used as a tool for the treatment of drug dependence (Bouso & Riba, 2014). Indeed, there are several clinics in South America that specialize in the treatment of drug dependence using ayahuasca, the most well-known being Takiwasi, in Peru (Mabit, 2007). In a recent study conducted with patients with severe depression, researchers found that ayahuasca activates a reward system in the brain called the *nucleus accumbens* (Sanches et al., 2016), creating an effect that the authors of the study found to be unique to patients with depression – a finding that contributes to explaining the anti-depressant effects of ayahuasca in patients with severe depression (see below).

One of the first human studies on ayahuasca use showed that many participants of UDV church rituals stopped using alcohol and other drugs, such as cocaine, as a result of their participation in church rituals (Grob et al., 1996). These findings were also found in a subsequent study with members of the Santo Daime church in Oregon, USA (Halpern et al., 2008). Another study with a large number of participants, which compared 127 ayahuasca users with 115 controls, failed to find evidence of drug dependence according to the biopsychosocial criteria of the ASI scale (Addiction Severity Index, the standard scale to assess drug dependence), or evidence that the continuous ritual use of ayahuasca was associated with harmful biopsychosocial consequences related to drugs of abuse. Moreover, the ayahuasca group consumed less alcohol and other drugs compared to the control group, and these scores on the biopsychosocial criteria for drug dependence were replicated a year later, confirming the consistency of the results (Fábregas et al., 2010). A study with adolescent members of the UDV church also found that the ayahuasca group consumed less alcohol than the control group, concluding that rather than being associated with drug dependence, ayahuasca use seemed to act as a protective factor regarding alcohol consumption (Doering-Silveira et al., 2005a).

Several new biomedical and ethnographic studies have been published in the last few years, that assessed the anti-addictive properties of ayahuasca. One study assessed the efficacy of a program in Peru that uses traditional Amazonian medicine, including ayahuasca, with patients who are dependent on multiple substances (mainly cannabis, alcohol and cocaine), found a significant decrease for addiction severity outcomes and increases in quality of life (Berlowitz et

al., 2019). Another study found a reduction in alcohol and tobacco use disorders among religious users of ayahuasca compared with the general population (Barbosa et al., 2018). An international survey of 96,901 people who have used various drugs showed that the sub-sample of ayahuasca users (500 people) reported having used less alcohol than those who used other psychedelics (such as LSD or psilocybin) and reported having the best quality of life of the entire sample (Lawn et al., 2017). Other recent studies showed evidence of efficacy in the treatment of drug dependence in different cultural populations and treatment settings (Fernández et al., 2015; Loizaga-Velder and Verres, 2014; Thomas et al., 2013). Two recent ethnographical studies aimed at studying the anti-addictive properties of ayahuasca found improved recovery in subjects as a result of participating in ayahuasca ceremonies (Talin & Sanabria, 2017; Apud & Romaní, 2017).

8. Therapeutic potential of ayahuasca

The therapeutic properties of ayahuasca are likely due to a combination of its psychoactive effect – and the associated subjective experiences – and its pharmacological actions. Ayahuasca activates brain areas related to the memory of personal events (the so-called episodic memory) and the awareness of emotions and internal sensations (Riba et al., 2006; de Araujo et al., 2011). From a psychological perspective, several recent studies have shown that the psychotherapeutic potentials of ayahuasca could be related to its capacity to increase what in clinical psychology is called “decentration” (Franquesa et al., 2018; Soler et al., 2016), or the ability to observe thoughts and emotions as transitory events of the mind without being trapped by them, mindfulness capacities and cognitive flexibility (Murphy-Beiner & Soar, 2020; Sampedro et al., 2017; Soler et al., 2018). These processes are seen as important in clinical psychology, since they are considered to be responsible for, and therefore explain, the psychotherapeutic results.

If ayahuasca does not have potential for recreational use or abuse, there must be other reasons why people use it. Personality studies performed among Brazilian and Spanish ayahuasca users did not find higher scores on a scale known as Novelty Seeking (Grob et al., 1996; Bouso et al., 2012; Bouso et al., 2015), a personality trait for which users of drugs of abuse have high scores. Nevertheless, ayahuasca users scored higher than controls on a personality trait called Self-Transcendence (Bouso et al., 2012; Bouso et al., 2015), or the tendency to have a transcendent concept of life, not necessarily associated with a religious affiliation. Taken together, these personality studies have found that people who use ayahuasca do so for reasons that are related to personal development, the search for psychological wellbeing, and adapting better to their environment. Indeed, these studies reported that ayahuasca users are people perfectly adapted and integrated in their social, working, and familiar environments and that ayahuasca is used as a tool for personal and spiritual improvement – findings that are similar to those observed among people who practice meditation or other techniques for personal development and wellbeing (Soler et al., 2016; Palhano-Fontes, 2015).

There are some studies that have explored the psychotherapeutic potential of ayahuasca in clinical populations. The most solid evidence is found in patients with resistant major depression. A recent study reported anti-depressant effects of ayahuasca in patients with major depression, effects that were sustained for 21 days after the administration of a single dose (Osório et al., 2015; Sanches et al., 2016). This therapeutic effect was associated with brain changes measured with neuroimaging techniques, thus providing an objective demonstration of therapeutic change (Sanches et al., 2016). Another more recent study confirmed the anti-depressant effect of a single dose of ayahuasca in a placebo-controlled clinical trial (Palhano-Fontes et al., 2017). In that clinical trial researchers also reported a decrease in suicidality ideation in the ayahuasca group

compared with placebo (Zeifman et al., 2019), a result that also found in another open study (Zeifman et al., 2020). Cortisol was also assessed, showing after ayahuasca treatment similar levels than normal subjects, which can be a biological marker of the reduction of depression and suicidal ideas (Galvão et al., 2018). Ayahuasca also increases the levels of neurotrophic factors (mainly BDNF or brain-derived neurotrophic factor), which are associated with neuroplasticity and antidepressant effects, among others (de Almeida et al., 2019).

Ayahuasca also induced changes in the inflammatory profile of patients with depression, suggested by decreased C-Reactive Protein concentrations after the ayahuasca session, which was correlated with the improvement of depressive symptoms (Galvao-Coelho et al., 2020).

Ayahuasca psychotherapeutic potential has been also investigated for the treatment of other psychological disorders. Two studies found positive outcomes using ayahuasca in grief therapy (González et al, 2019; González et al., 2020), with one documenting persistent effects at one-year follow-up (González et al., 2020). Two preliminary studies have reported positive results in patients with eating disorders (Lafrance et al., 2017; Renelli et al., 2018). Although the research on the therapeutic effects of ayahuasca is still nascent, several authors propose that ayahuasca could also be used to treat post-traumatic stress disorder (PTSD) (Nielson and Megler, 2013), in borderline personalities (Domínguez-Clavé et al., 2019), or for the treatment of antisocial behavior, among other disorders of our civilization (Frecksa et al., 2016), including the improvement of symptomatology of some severe physical conditions such as amyotrophic lateral sclerosis (ALS) (ALS Untangled Group, 2017). Along that line of enquiry, several studies have assessed *in vitro* the potential neuroprotective properties of ayahuasca compounds. In one of those studies, harmine showed proliferation of human neural progenitors (Dakic et al., 2016). In yet another study, harmine, harmaline, and tetrahydroharmine (the three main constituents of *B. caapi*) were found to stimulate adult neurogenesis (Morales-García et al., 2017). In the late 1920s, both Louis Lewin and Kurt Beringer reported promising effects of harmine for the treatment of Parkinson Disease (PD) and recently examinations into the potential role of *B. caapi* in the treatment of PD and other neurodegenerative diseases were revived (Djamshidian et al., 2015; Fisher et al., 2018).Two independent studies have also shown that DMT produces neurogenesis and neuroprotection both in cell cultures (Berthoux et al., 2019) and in animals (Morales-García et al., 2020). In summary, ayahuasca is showing promising results not only in treating psychological conditions, but also as a neuroprotective and in promoting neurogenesis.

9. Analytical reports

There are several studies that have analyzed ayahuasca's alkaloid content. The levels of alkaloids can vary depending on different parameters, such as the preparation method (Hamill et al., 2019). However, the alkaloid content seems to be less affected by differences such as the season or the region where the plants are harvested (Wang et al., 2010).

Gable (2007) published a reviewed of several scientific publications in which researchers analyzed ayahuasca samples. The author reported that a typical dose of ayahuasca (100-150 mL) contained a range between 8.8 mg and 42 mg of DMT, while a few years later Gaujac et al. (2012) reported DMT concentrations ranging from 25.5 mg to 171 mg of DMT per 150 mL dose. McKenna et al. (1984) reported DMT concentrations between 0.13-0.30 mg/mL and Callaway (2005) of 0-14.1 mg/mL. Lanaro et al. (2015) also analyzed the DMT concentration found in samples used by Brazilian churches and reported an amount of 0.82 mg/mL, which is equivalent to 82.3 mg of DMT per 100 mL dose. Uthaug et al. (2018) analyzed four different ayahuasca

samples (two from Holland and two from Colombia) and found that in a dose of 100 mL there were 185.8 mg and 457.7 mg of DMT in the case of the Dutch samples; and 94.7 mg and 250.2 mg of DMT in the case of Colombian ones. Souza et al. (2019) analyzed 38 ayahuasca samples, reporting concentrations ranging from 0.62 to 3.40 mg/mL. Santos et al. (2020) found 0.10-3.12 mg/mL in 33 ayahuasca samples. Lastly, Kaasik et al. (2020) analyzed 102 ayahuasca samples, reporting DMT values ranging from 0 to 2.68 mg/mL. With regard to harmaline, Gable (2007) analyzed samples in which 17 mg to 280 mg of harmine, 4.6 to 28 mg of harmaline and 4.2 to 150 mg of tetrahydroharmine were found. In McKenna et al. (1984), 0.15-0.34 mg/mL of harmine, 0-0.20 mg/mL of harmaline, and 0.05-0.80 mg/mL of tetrahydroharmine were found. Callaway reported values of 0.45-22.8 mg/mL of harmine, 0-0.9 mg/mL of harmaline, and 0.48-23.8 mg/mL of tetrahydroharmine. Uthaug et al. (2018) reported that the Dutch samples contained 242.7 and 485.9 mg of harmine and 446 mg and 19 mg of harmaline per dose (100 mL), while the Colombian samples contained 630.8 mg and 413.7 mg of harmine and 34.9 mg and 28.7 mg of harmaline per dose (100 mL). In the samples analyzed by Souza et al. (2019) 4.14-18.16 mg/mL of harmine, 0.40-3.92 mg/mL of harmaline, and 4-30.8 mg/mL of tetrahydroharmine were observed. Santos et al. (2020) reported 0.11-7.11 mg/mL of harmine, 0.01-0.94 mg/mL of harmaline, and 0.09-3.05 mg/mL of tetrahydroharmine. In the 102 samples analyzed by Kaasik et al. (2020), amounts of 0.06-4.44 mg/mL of harmine, 0-0.33 mg/mL of harmaline, and 0.01-3.87 mg/mL of tetrahydroharmine were found.

In the case of some clinical trials in which ayahuasca has been administered, Riba et al. (2003), administered low and high doses of ayahuasca. For low doses, they used 0.6 mg of DMT, 1.0 mg of harmine, 0.07 mg of harmaline and 0.82 mg of tetrahydroharmine. For high doses they used 0.85 mg of DMT, 1.4 mg of harmine, 0.09 mg of harmaline and 1.16 mg of tetrahydroharmine. In Riba et al. (2004), only high doses were used: 0.85 mg/kg of DMT, 1.4 mg/kg of harmine, 1.15 mg/kg of tetrahydroharmine and 0.9 mg/kg of harmaline. In subsequent studies of the same group, an even higher dose of DMT (1 mg/kg) was used (Barbanoj et al., 2008; dos Santos et al., 2011).

In later studies carried out by researchers in Brazil, local religious groups provided the ayahuasca, which was analyzed and different concentrations of active components were found. For instance, in Sanches et al. (2016) the ayahuasca used had 0.80 mg/mL of DMT, and 0.21 mg/mL of harmine. In Palhano-Fontes et al. (2019), the ayahuasca used shown 0.36 mg/mL of DMT, 1.86 mg/mL of harmine, 0.24 mg/mL of harmaline, and 1.20 mg/mL of tetrahydroharmine. Lastly, Rocha (2020) reported values of 0.67 mg/mL of DMT, 0.87 mg/mL of harmine, 0.27 mg/mL of harmaline, and 0.38 mg/mL of tetrahydroharmine.

10. Ayahuasca and public health

In addition to the scientific evidence that shows promising results regarding ayahuasca's therapeutic properties, there is a concern that must also be considered. Ayahuasca is not only used in controlled clinical settings, but also in ceremonial contexts where participants are not always subject to adequate screening processes to exclude individuals with a higher risk of developing serious adverse reactions, such as psychotic or bipolar outbreaks or pharmacological interactions. In short, the question that must be addressed is: What are the implications of ayahuasca use for public health? In a recent study conducted in Spain (Ona et al., 2019), 380 regular participants of ayahuasca ceremonies were interviewed face-to-face using public health indicators, along with indicators of community ties, stress-coping strategies, values, and psychosocial well-being. The results were compared with the normative data of the general Spanish population. Regular use of ayahuasca was associated with a greater positive perception

of health and a healthy lifestyle, among other results. Fifty-sex percent of the sample reported having reduced their use of prescription medications since they started participating in ayahuasca ceremonies. Participants who had used ayahuasca more than 100 times scored higher on personal values indicators. The main conclusion of this study is that a respectful and controlled use of ayahuasca taken in community settings can be incorporated into modern society with benefits for public health. This new approach, based on the use of public health indicators not previously used in ayahuasca studies, offers relevant information on the impact of long-term exposure to ayahuasca on public health.

Conclusion

In conclusion, both the scientific literature existing to date on acute and long-term effects of ayahuasca and the studies in which ayahuasca has been used as a therapeutic tool in psychiatric population, show that the decoction or admixture is physiologically and psychologically safe and, additionally, that it has interesting therapeutic potentials. The main medical conditions for which ayahuasca is being studied (mental disorders and neurodegenerative diseases) currently lack effective treatments. Added to the wide safety profile of ayahuasca, this fact justifies future studies to provide information on its clinical efficacy.

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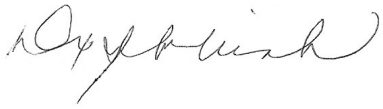

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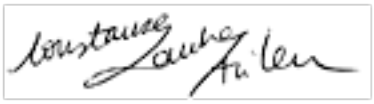

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