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REVIEW ARTICLE

Ayahuasca: Psychological and Physiologic Effects, Pharmacology and Potential Uses in Addiction and Mental Illness

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Abstract: ***Background*:** Ayahuasca, a traditional Amazonian decoction with psychoactive properties, is made from bark of the *Banisteriopsis caapi* vine (containing beta-carboline alkaloids) and leaves of the *Psychotria viridis* bush (supplying the hallucinogen N,N-dimethyltryptamine, DMT). Originally used by indigenous shamans for the purposes of spirit communication, magical experiences, healing, and religious rituals across several South American countries, ayahuasca has been incorporated into folk medicine and spiritual healing, and several Brazilian churches use it routinely to foster a spiritual experience. More recently, it is being used in Europe and North America, not only for religious or healing reasons, but also for recreation.

***Objective*:** To review ayahuasca's behavioral effects, possible adverse effects, proposed mechanisms of action and potential clinical uses in mental illness.

***Method*:** We searched Medline, in English, using the terms ayahuasca, dimethyltryptamine, *Banisteriopsis caapi*, and *Psychotria viridis* and reviewed the relevant publications.

***Results*:** The following aspects of ayahuasca are summarized: Political and legal factors; acute and chronic psychological effects; electrophysiological studies and imaging; physiological effects; safety and adverse effects; pharmacology; potential psychiatric uses.

***Conclusion*:** Many years of shamanic wisdom have indicated potential therapeutic uses for ayahuasca, and several present day studies suggest that it may be useful for treating various psychiatric disorders and addictions. The side effect profile appears to be relatively mild, but more detailed studies need to be done. Several prominent researchers believe that government regulations with regard to ayahuasca should be relaxed so that it could be provided more readily to recognized, credible researchers to conduct comprehensive clinical trials.

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1. INTRODUCTION

For the current review, we searched Medline, in English, with the terms "ayahuasca," "dimethyltryptamine," "N,N-dimethyltryptamine," "*Banisteriopsis caapi*," and "*Psychotria viridis*". In addition, we reviewed relevant and interesting references from the articles collected, including some references to books or sections of books.

Ayahuasca, meaning "vine of the soul" or "vine of the dead" in the Quecha language, is a traditional Amazonian decoction also known by the names of hoasca or oasca (the Portuguese transliteration), caapi or kahpi, daime (which means "give me" in Portuguese), yajé or yage, cipó, natema or natem, dapa, mihi, or vegetal [1, 2]. The psychoactive drink is made from the stem bark of the *Banisteriopsis caapi* vine, rich in beta-carboline harmala alkaloids, usually in combination with N,N-dimethyltryptamine (DMT)-containing leaves of the *Psychotria viridis* bush [3]. The harmala alkaloids harmine and harmaline are monoamine oxidase inhibitors (MAOIs), without which the DMT would be inactivated by the gut and liver MAOs, while tetrahydroharmine acts as a weak serotonin reuptake inhibitor without any MAOI action [4]. The combined action of the two plants has been empirically understood by Amazonian indigenous populations for at least 3000 years [5]. Originally used by Amazonian shamans in ritual ceremonies and by folk healers for a variety of psychosomatic complaints [6], worldwide

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interest in ayahuasca has been rising. It is now being used as a sacrament by three Brazilian churches, by tourists seeking a spiritual experience, and by recreational users all over the world. With growing interest and increasing use of ayahuasca, it is important to understand the safety, behavioral effects, and potential clinical uses. Research into medical use of ayahuasca indicates potential as a treatment in addictions, depression and anxiety [7], with a variety of other possible medical uses, though these require more research.

The use of ayahuasca dates back to the earliest aboriginal inhabitants of the Amazonian basin, where it was used by indigenous shamans for communication with spirits, magical experiences, rites of initiation, and healing rituals [8]. Ayahuasca was held in high regard among these populations, particularly for religious and healing purposes. These were small private ceremonies where the patient and the shaman, and perhaps one or two others, would consume ayahuasca. Shortly after consumption, vomiting and often intense diarrhea occur. But after this, visions begin to appear, and the nature of the disease and curative plants are revealed to the shaman and the patient [9]. Over the past several hundred years, the use of ayahuasca spread into Peru, Colombia, and Ecuador among indigenous Mestizo populations where it was integrated into folk medicine [8]. These practices evolved during the early 1930s [10] for use as a sacrament in three Brazilian syncretic churches which combine indigenous and Christian traditions, the União do Vegetal (the largest, more meditative), the Santo Daime (the oldest, livelier, with music), and Barquinha (an Afro-Brazilian church), during twice monthly ceremonies lasting approximately four hours [2, 4, 11-13]. Ayahuasca therapy has been used by witch doctors in treating addictions, and Lemlij [14] describes a group therapy model where participants come as many weeks as they need and may make a voluntary monetary contribution at the end.

The drink is becoming more popular in North America, Europe and beyond for religious, spiritual, and recreational use [2], so it is important that medical practitioners be aware of the subjective and objective effects that could affect patients they may see and understand any adverse effects, as well as explore potential medical uses. While a considerable amount of modern use of DMT and ayahuasca is for recreational purposes, Cakic *et al*. [15] found that a group of Australian users gained psychotherapeutic benefits from use. Cardenas and Gomez [16] examined motives for modern urban use by 40 residents of Bogota, Colombia. They found that subjects used ayahuasca to achieve mental wellbeing and also to enhance their ability to solve personal problems; in another study, the participants cited "healing" and "equilibrium" as reasons for use [17]. Kjellgren *et al*. [2] found similar motives among northern European users, including exploring their inner world, personal development, increasing self-awareness, examining psychological patterns, and enhancing creativity. Fiedler *et al*. [18] studied motives for use among Santo Daime members, and found that reasons were consistently religious or spiritual, as well as self-treatment.

Travelling in search of a transformative hallucinogenic experience is referred to in the literature as drug tourism, spiritual tourism, or modern shamanic tourism. Ayahuasca tourism is growing in popularity, and most often this involves nonindigenous tourists going on all-inclusive trips to the Amazon to partake in a shaman-led ayahuasca ceremony [19]. One article analyzes the internet's role in the evolution of ayahuasca tourism, specifically by examining the website of one such tour company, Blue Morpho Tours, and suggests that such experiences represent the quest for "the authentic, ethnic Other" [19]. Modern shamanic tourism is discussed in a dissertation by Fotiou [20] and in articles by Winkelman [21] and Arrevalo [22], both of whom collected data showing that motivations to participate in such an experience are usually not excuses for drug experimentation, but are genuinely sought out as spiritual pilgrimages.

Kavenska and Simonova [23] examined the motivations, perceptions, and personality traits of 77 study participants who had gone to South America to use ayahuasca. Motivations included "curiosity, desire to treat mental health problems, need for self-knowledge, interest in psychedelic medicine, spiritual development, and finding direction in life". Reported benefits included self-knowledge, improved interpersonal relations, and gaining new perspectives on life. Participants scored significantly above average on the Personality Style and Disorder Inventory (PSSI, Persönlichkeits-Stil- und Störungs-Inventar) scales of "intuition, optimism, ambition, charm, and helpfulness and significantly lower on the scales of distrust and quietness". While most experiences of this variety with ayahuasca are relatively safe, Arrevalo [22] warns against inexperienced or false shamans using toxic plants as additives to the ayahuasca preparation. Balikova [24] reports on a "meditation session" in Prague in 2001 (named "releasing autohypnosis of forest medicine men") that ended with many of its participants hypotensive, hyperthermic, with some even requiring mechanical ventilation. This was attributed to a synergistic effect between harmine and two anticholinergics, atropine and scopolamine, found in the brew allegedly made from plants named "Ikitos" or "Toe". However, these anticholinergics are not found in ayahuasca.

Alexander Shulgin synthesized and personally tried hundreds of psychoactive substances. He and his wife, Ann Shulgin, wrote the book TIKHAL (Tryptamines I have known and loved), which contains a fictionalized autobiography and essays, along with a synthesis manual for 55 substituted tryptamines, and dosing suggestions and accounts of the subjective experience of taking these substances [25]. Research into ayahuasca really took off in 1993, when a multidisciplinary team began a comprehensive investigation into the immediate physiologic and psychological effects as well as the pharmacology of ayahuasca use in 15 male long term (greater than 10 years) adult members of the União do Vegetal church (UDV) called the Hoasca Project, which was conducted by an international team of researchers in the city of Manaus, Brazil [4, 8]. It was an observational study that compared these users with 15 matched male nonusers, and revealed some interesting and surprising results. Long term users scored slightly higher on cognitive tests than nonusers, and many users reported ayahuasca and UDV membership as having a very positive impact on their lives; in fact many reported that they were able to completely turn their lives around from previous dysfunctional behaviours such as alcoholism, violence, dishonesty and infidelity, and they lived

happier, more meaningful lives. In addition, there were no signs of acute toxicity or adverse effects on health from ayahuasca use reported [10].

At a 2010 conference organized by the Multidisciplinary Association for Psychedelic Studies (MAPS), ayahuasca became one of the main topics of the conference because presenters submitted such high numbers of proposals on the topic [26]. As ayahuasca use spreads, interest among the general public is increasing as well. Ayahuasca was the subject of a 2011 episode of David Suzuki's "The Nature of Things" on the Canadian Broadcasting Corporation network. Araujo *et al*. [27] provide a broad update on hallucinogens. New psychoactive substances continue to be synthesized, greater than 300 of them since the year 2000. Users are obtaining a variety of synthetic or naturally sourced substances through the internet or through specialized shops. They are often sold as "research chemicals" or "legal highs," and labelled "not for human consumption". Kowalczuk *et al*. [28] were able to purchase dried *P. viridis* leaves over the internet from several sources in Brazil, Peru, and Hawaii, and found that not all the specimens contained DMT. The authors concluded that proper identification and sale of *P. viridis* are problematic, and suggested that legislation regarding both DMT and *P. viridis* needs to change.

2. POLITICAL AND LEGAL FACTORS

In 1970, DMT was classified as a Schedule I drug under the US Controlled Substances Act [27]. 1971 was the year of the United Nations (UN) treaty, the Convention on Psychotropic Substances, which replaced the Single Convention on Narcotic Drugs of 1961. UN Schedule I drugs are deemed to have no medicinal value, and include MDMA (3,4-methylenedioxymethamphetamine), psychedelics, and cannabinoids, and it is puzzling that far more dangerous drugs such as cocaine, methamphetamine, and opioids are categorized as Schedule II [28]. The International Narcotics Control Board is currently the control body in charge of implementing the conventions [29, 30]. These classifications have nearly halted research into many potential valuable treatments for a wide range of conditions. Not until 1987 was the use of ayahuasca in a religious context protected by Brazilian law [8, 31]. Members of the American ayahuasca churches kept their use quiet until 1999 when the United States' Drug Enforcement Administration (DEA) confiscated ayahuasca that had been smuggled in. The UDV began a federal lawsuit in 2000 [32], where under the Religious Freedom Restoration Act of 1993, they argued they could use ayahuasca on the basis of religious freedom, and the courts agreed [1]. The federal government appealed the decision several times until, in 2006, the US Supreme Court unanimously decided to allow the ceremonial use of ayahuasca in the UDV church, as they were unable to demonstrate that it had any detrimental effects [3, 33]. The Santo Daime religion fought a similar battle in Oregon, likely benefitting from the precedent set by the UDV church, and won an injunction allowing ceremonial use of ayahuasca in 2009. Even before that, the Oregon State Board of Pharmacy concluded in 2000 that in the Santo Daime religion, ayahuasca had a "nondrug" use, and was not subject to state regulation [1]. A topic of heated debate, the Brazilian government decided in 2010 that for pregnant women and children to consume ayahuasca is an "exercise of parental rights" [12].

In Canada, the Controlled Drugs and Substances Act is the federal law enacted in 1996 that regulates a great variety of illicit psychoactive substances, including opioids, hallucinogens, cannabis, and cocaine in accordance with international laws. Interestingly, there is a clause which allows certain exemptions, called Section 56.

"The Minister may, on such terms and conditions as the Minister deems necessary, exempt any person or class of persons or any controlled substance or precursor or any class thereof from the application of all or any of the provisions of this Act or the regulations if, in the opinion of the Minister, the exemption is necessary for a medical or scientific purpose or is otherwise in the public interest."

Interestingly, compounds found in ayahuasca are controlled substances under the Controlled Drugs and Substances Act (CDSA), but the plants containing the substances are not. As an example, this is unlike cocaine, as both the plant itself, *Erythroxylum coca*, and the substance itself are both listed. A Canadian branch of the Brazilian Santo Daime church in Montreal, called the Céu do Montreal, sought an exemption from the Canadian Controlled Drugs and Substances Act in 2001, and in 2006, Health Canada in fact decided to authorize the church to import ayahuasca in the form of tea [34].

Gabor Maté, a Canadian physician, researcher, speaker, and columnist, held multiple day "Working with Addiction and Stress" retreats, which included 4 days of group therapy and two expert-led ayahuasca ceremonies in 2009 and 2010. The team holding the retreat included ayahuasca ceremonial leaders from Peru and Canada (British Columbia), and the participants were from the general Canadian public. In this small study, (N of 12 with no matched controls) data indicated reduced alcohol, tobacco and cocaine use from 6 month followup self-reports, but not for marijuana or opioids. As well, various validated scales pointed towards statistically significant improvements in hopefulness, empowerment, mindfulness, and quality of life [35]. In November 2011, Health Canada determined that Dr. Maté should discontinue his retreats, and in October 2012, the Health Minister determined that ayahuasca use, even ceremonial, was not in the best interest of the public [35].

Indeed more and more people are feeling compelled to speak up on behalf of religious and ceremonial use of ayahuasca and to speak out against government drug policies that hinder scientific research of hallucinogenic substances, just as scientists did in a 1951 "Statement on Peyote" regarding the use of peyote by the Native American Church. In their "Statement on ayahuasca," Anderson *et al*. [36] argue that current policies are not based on scientific evaluations and add that sensationalized media portrayals of ayahuasca as a street drug have not aided the cause.

3. PSYCHOLOGICAL EFFECTS

3.1. Acute Psychological Effects

The ayahuasca experience begins approximately 40 minutes following ingestion, peaking between 60 and 120

minutes, with subjective effects fading by approximately 4 hours. Mabit [5] reports that ayahuasca users do not lose consciousness but experience alterations in it, while Strassman [37] reported that with IV DMT injection, users experience a transient loss of their normal awareness lasting only a few minutes, with effects subsiding almost completely in half an hour. Some of the psychological effects during ayahuasca ingestion are reported by Mabit [5] and include a powerful sense of self-confidence, a new perspective and reinterpretation of intrapsychic conflicts; users may reveal intimate truths, and ayahuasca may be powerful in facilitating psychotherapy.

Kjellgren *et al*. [2] described the "transcendental circle," a cycle of experiences consistent among different users following ayahuasca ingestion. Approximately 30 minutes after ingestion, subjects noted changing perceptions and shaking, and felt vulnerable and easily influenced. Shortly after, participants developed feelings of confusion, paranoia and fear; psychological defenses were diminished and participants experienced traumatic memories and gained new insight into personal matters [38]. This terrifying state peaks with intense vomiting, after which most participants noted an abrupt shift into an expansive state. Participants describe a transcendental experience in a spiritual world, encountering plant and animal spirits and even contact with a higher power, feelings of oneness with the universe, profound peace and ecstasy, and newly gained understandings of death and what comes after. Sense of time is altered, and users experience feelings of timelessness, time speeding up or slowing down, or traveling in time [39, 40]. Users remain aware of their surroundings and are able to speak [3]. Beyer [41] refers to a similar pattern and describes three phases, the first with visual imagery and sometimes nausea or vomiting; the second phase is contact with a spiritual world in which users report useful lessons from spirit teachers, and the third phase involves fading visuals and feeling physically drained.

Several studies used the Hallucinogen Rating Scale (HRS), which measures subjective effects of psychedelic ingestion on six scales, including Somaesthesia (somatic effects), Affect (emotion and affect), Volition (willful desire to interact), Cognition (thought process and content), Perception (sensory experiences), and Intensity (the strength of the experience). This rating scale was developed by Dr. Rick Strassman, and is loosely based on the components of the mental status exam [37]. Riba *et al*. [13] found that at least 75% of 18 healthy volunteers with experience in psychedelic use responded positively to 14 selected items in the HRS with a dose of 0.85 mg of DMT/kg of body weight, and described the effects of increased activation, euphoria, and wellbeing. They also reported perceptual changes and increased emotional lability. They also found a correlation between subjective effects of DMT and plasma concentration, and both peaked between 1.5 and 2 hours. Significant dose-dependent increases in all scores on subscales of the HRS have been found [42-44]. When compared to IV DMT, ayahuasca produced a relatively mild high as measured by the HRS [8].

With regard to visual effects, objects appear to vibrate or increase in brightness, colours intensify, moving geometric patterns and intricate images occur with eyes closed or open [3]; kaleidoscopic imagery or visions of people, beautiful scenery, or snakes or jungle animals are common [38, 45, 46]. Effects peak between 60 and 120 minutes [47]. Visual creativity may be heightened for some time even after acute effects wear off [48]. Visual phenomena tend to linger even after acute effects subside, and this may be related to neurochemical changes in the visual cortex and the claustrum. The claustrum, a serotonergic nucleus in the brain, connects nearly all parts of the cerebral cortex. It is theorized that cortical areas with related functions tend to have overlapping claustral projections. Layer 6 (innermost) of the visual cortex and the claustrum have parallel circuits, both of which generate end-inhibition of layers 1 to 4 of the visual cortex through inhibitory interneurons. LSD and other hallucinogens are thought to also excite these inhibitory interneurons. Layers 1 to 4, important in interpreting shorter lines, have a property called end-stopping, in which they respond to lines up to a certain length; beyond these lengths, they are inhibited. Uncoupling of claustral and visual cortex sources of edge information, along with abnormal end-stopping properties and erroneous signalling, may explain some of the well known effects like trails, halos, wavy edges, and misinterpretation of contours [48]. Synesthesia is common, particularly auditory to visual synesthetic effects, and usually they are associated with music. The tempo and feel of the music are often reflected in the movements of the visions and how often the images change [49]. Shanon [49] also noted enhanced improvisation and improvements in their ability to play their instruments by the musicians during Santo Daime rituals, as well as in himself at the piano.

3.2. Long-term Psychological Effects

Grob *et al*. [8] performed a small study comparing 15 syncretic church ayahuasca users versus 15 matched controls as a part of their Hoasca Project. They found that among the ayahuasca users, all alcohol, depressive, and anxiety disorders remitted after joining the UDV. As with the adolescent studies, it is hard to separate the effects of a strong supportive community and religious belonging from the actual effects of the substance, and to determine whether people with particular traits are drawn toward ayahuasca use or church involvement. In the same study, the Tridimensional Personality Questionnaire revealed that users scored significantly lower in the areas of novelty seeking and harm avoidance, but similarly on reward dependence compared to controls [50]. On neuropsychological testing with the World Health Organization, University of California, Los Angeles Auditory Verbal Learning Test (WHO-UCLA AVLT), users scored significantly higher in the area of word recall on the fifth trial. They also scored better in number of words recalled, delayed recall, and words recalled after interference, though these were not statistically significant. Grob *et al*. [8] reported that long term ceremonial use does not appear to negatively affect neuropsychological function [8]. Regular users of ayahuasca scored lower on two of the Addiction Severity Index subscales, Alcohol Use and Psychiatric Status, and ritual use does not seem to be associated with the negative psychosocial impacts of many other drugs of abuse [51]. Of 32 members belonging to the American Santo Daime church, 19 reported previous psychiatric histories, but all reported good mental health and only two currently had an active

psychiatric disorder [1]. Harris and Gurel [52] reported that ayahuasca users scored higher in the areas of Joy in Life and Relationship to the Sacred, and had an experience just as spiritual as the Catholic retreat participants, and also had reduced alcohol consumption, healthier eating, better mood, and self-acceptance.

Barbosa *et al*. [17] reported on 23 subjects just prior to their first ayahuasca experience in a religious setting and six months following, using three surveys, the Clinical Interview Schedule-Revised Edition (CIS-R), Short Form-36 Health Survey (SF-36), and the Temperament and Character Inventory-125 items (TCI-125). They found no adverse effects on quality of life, measured by the CIS-R, and some participants showed significant improvements in mental health on the SF-36 as well as in minor psychiatric symptoms on the CIS-R. They also found that regular users (>9 sessions in six months) scored significantly higher on social and emotional functioning domains of the SF-36 questionnaire than less frequent users. In a previous study, Barbosa *et al*. [11] reported on 28 first time ritual users and also found the same reduction of minor psychiatric symptoms in a shorter time frame of 1 to 2 weeks following use. In another more recent study, Barbosa *et al*. [53] looked at regular ayahuasca users within a religious setting. Using assessments including the Profile of Mood States (POMS), Big Five Inventory (BFI), Medical Outcomes Study Short Form-36 (SF-36), Addiction Severity Index (ASI), and the California Verbal Learning Test (CVLT), the authors showed that the regular ayahuasca users scored better in terms of mood, having more positive personality traits, better health, improved addiction problems, and better scores on the CVLT. Barbosa *et al*. [53] concluded that religious use of ayahuasca "does not adversely affect neuropsychological functioning and may have positive effects on substance abuse and mood". One study assessed the effects of ayahuasca on creativity using the Torrance Tests of Creative thinking, and found that ingestion had no effect on the areas of "fluency," "relative flexibility," or "relative originality"; however, it increased participants' ability to come up with "highly original solutions" to tasks [54]. In addressing the possibility that more creative individuals may seek out a consciousness-altering experience, they found that baseline creativity scores did not differ when compared to controls. Soler *et al*. [55] found that ayahuasca intake resulted in increased decentering ability (measured by the Experiences Questionnaire), as well as reduced inner reactivity and reduced judgmental processing of experiences on the Five Facets Mindfulness Questionnaire.

In a 2012 study, Bouso *et al*. [56] compared a variety of psychological measures in ayahuasca users against matched controls. They found that ayahuasca users scored lower on psychopathology measures (on The Symptom Check-List-90-Revised/SCL-90-R psychopathology questionnaire), performed better on cognitive tests (such as the Stroop Colour and Word Test and the Wisconsin Card Sorting Test), and scored higher on the Purpose in Life Test, Spiritual Orientation Inventory, and Psychosocial Well-Being Test. These differences remained the same at one year followup, and there was no evidence of any deleterious effect on mental health and no signs of cognitive impairment among ritual ayahuasca users. Kuypers *et al*. [57] looked at ayahuasca's effect on creative divergent thinking, a way of thinking believed to enhance psychological flexibility and allow for new cognitive, emotional, and behavioural strategies. Assessing participants before and during the acute effects of ayahuasca, the authors found significantly increased divergent thinking while the subjects were on ayahuasca, and suggested this may facilitate psychotherapeutic interventions. In a research study based on results from the Ayahuasca Researcher's Behavioral Observation Scale (ARBOS), Shamanic Experience and Net Benefit scales, and the Temperament and Character Inventory Predictor scale, Burton [58] suggests we can predict which patients would benefit from or be harmed by participating in an ayahuasca ceremony.

In a questionnaire, 25 Northern European ayahuasca users reported increased self-awareness, being more loving, more empathetic, having greater creativity and new interests especially with nature, and having a more meaningful inner world [2]. Winkelman [21] reported similar effects including new insights and access to deeper levels of the self. Serious reflection on life, nature, and consciousness were consistent themes [3]. Cakic *et al*. [15] reported that increased "psychospiritual insight" was the most commonly reported positive effect among 12 Australian recreational DMT users, a finding in keeping with studies of religious and ceremonial ayahuasca use. Many users reported that prior to entering the church, they had alcohol problems and violent behaviour, and described themselves as impulsive, disrespectful, oppositional, and irresponsible. All 15 members involved in the Hoasca Project reported that ayahuasca had a profound influence on their lives, allowing them new insight into their self-destructive ways and motivating them to take control of their lives. They also reported better memory and concentration, and a consistently positive mood; however they all recognized the importance of the sense of community and guidance provided by ritual use within the church [8].

Dr. Jacques Mabit runs an addiction clinic in Peru and uses ayahuasca as a part of the treatment. He reports many positive effects: that ayahuasca increases intellectual capacity and concentration, reduces anxiety, increases tolerance of frustration, improves self-esteem, facilitates individuation processes, allows users to see beyond their own worldview and increases openness to new perspectives. Reports from his patients indicate that ayahuasca facilitates introspection and self-discovery, forgiveness without blame, recognition of mistakes, improved decision making ability, motivation to change, increased quality and quantity of dreams, reflections on life as a part of nature and discovery of previously unknown dimensions of life. As well, users seem to benefit from a structured, spiritual, religious, ritual manner of use [5]. Loizaga-Velder and Verres [59] interviewed 14 ritual participants who had long histories of severe substance dependence, and many had several unsuccessful treatments prior to ayahuasca assisted therapy. All participants reported ayahuasca rituals were pivotal to attaining abstinence or achieving less harmful patterns of drug use; they also reported ayahuasca was instrumental in understanding the causes of their addictions. Over half reported reduced cravings. In a study by Cavnar [60], self-identified gay and lesbian ayahuasca users reported feeling affirmation of their sexual orientation.

4. ELECTROPHYSIOLOGIC STUDIES AND IMAGING

4.1. EEG Studies

Using topographic quantitative electroencephalography (QEEG), Riba *et al*. [61] found patterns in line with previously described EEG findings for other psychedelics, and that ayahuasca shares EEG features with other serotonergic and dopaminergic drugs. The changes occurred as early as 15-30 minutes, peaked between 45 and 120 minutes, and then by 4-6 hours were at baseline. There was a decrease in absolute power in all bands, particularly the theta band. They also found dose-dependent decreases in power density in alpha-2, delta, and beta-1 frequency bands, and these were found mainly in the temporo-parieto-occipital junction, whereas similar findings were found for theta waves in the temporomedial cortex and frontomedial regions. A mild increase in relative global beta power was found with ayahuasca consumption; there were significant relative increases in power in the faster beta-3, beta-4 and beta-5 bands on EEG, and these were more intense and longer in a dose-dependent manner [42-44, 62, 63].

Schenberg *et al*. [64] showed a biphasic effect of ayahuasca on EEG, with reduced power in the alpha band (8-13 Hz) found 50 minutes after ingestion, and this effect was mainly found at the left parieto-occipital cortex. In the range 75 to 125 minutes, increased slow gamma power (30-50 Hz) was found at the left centro-parieto-occipital, left fronto-temporal and right frontal cortices. Fast gamma increases were observed at the left centro-parieto-occipital, left fronto-temporal, right frontal, and right parieto-occipital cortices [64]. Another study found that ayahuasca increases power in the 36-44 Hz band from the left occipito-temporal-parietal scalp electrode particularly with eyes closed, and hypothesizes the link between theories of the role of 40 Hz brain activity in consciousness and the location of the activity being consistent with ayahuasca's ability to enhance visual imagery [65]. As well, they found increases in 14-30 Hz beta bands. Confirming these findings, Stuckey [66] also reported similar findings in the 50-64 Hz bands, frequencies implicated in cross-modal sensory processing, and hypothesized a link between this and the intense synesthesia experienced during ayahuasca experiences. Valle *et al*. [67] noted ayahuasca induced decreases in power in delta, theta, and alpha frequency bands on EEG, and found that alpha band current density in parietal and occipital lobes was inversely correlated with intensity of the visual imagery.

Alonso *et al*. [68] mentioned some of these recent studies which highlight several of the same ayahuasca-induced EEG changes, such as decreases in current density in the frontomedial regions, but explained that hallucinogen-induced changes in frontal to posterior interactions are only starting to be explored. They used EEG and transfer entropy, a measure of the directional transfer of information between two processes. Transfer entropy analysis showed that frontal sources had decreased influence over central, parietal, and occipital locations, and posterior locations had increased influence over frontal signals. The authors noted a correlation between intensity of subjective effects and decreases in anterior-to-posterior transfer entropy, and postulated that psychedelics confer their effects in part by disrupting the normal state of top-down neural control and allowing greater bottom-up transfer of information in the human brain. The timing of these transfer entropy findings coincided with subjective effects and DMT plasma concentrations.

4.2. Single Photon Emission Computed Tomography

In a study of cerebral blood flow using single photon emission computed tomography (SPECT) with 15 male volunteers, Riba *et al*. [69] reported that ayahuasca produced an activation of frontal and paralimbic brain regions and increased blood perfusion bilaterally in the anterior insula; greater intensity was observed in the right hemisphere and in the anterior cingulate and frontomedial cortex of the right hemisphere (areas involved in somatic awareness, subjective feelings, and arousal of emotion). Additional increases were observed in the left amygdala and parahippocampal gyrus, a structure also involved in emotional arousal. Sanches *et al*. [70] reported increased blood perfusion in the left nucleus accumbens, right insula, and left subgenual area eight hours after ayahuasca ingestion and that ayahuasca was well tolerated. Riba *et al*. [69] indicated that these findings suggest an interaction of ayahuasca with neural systems is important in introspection and processing of emotion and imply a modulatory role of serotonergic neurotransmission in these processes.

4.3. Magnetic Resonance Imaging

Ayahuasca causes a statistically significant increase in activation of many occipital, temporal, and frontal areas, including the primary visual area on magnetic resonance imaging during closed eye imagery [71]. Even with eyes closed, on ayahuasca the levels of activation in the visual area were consistent with seeing a natural image. This action was seen bilaterally in the occipital cortex, which includes Brodmann areas (BA) 17, 18, 19, all involved in vision. BA 17 has also been correlated with perceptual changes and psychotic effects such as hallucinations. Areas involved in episodic memory were also activated, including the parahippocampal gyrus (BA 30) and the middle temporal cortex (BA 37). The frontal cortex (BA 10) is also activated. Emotions and memories were intensified and past experiences were seen through vivid imagery, which gave the whole experience a "status of reality" [71]. The posterior cingulate cortex (PCC) is key component of the default mode network, a group of neural pathways involved in inwardly focussed thought, conception and awareness of self, remembering the past and envisioning the future. Bousa *et al*. [72] found an inverse correlation between cortical thickness in the PCC and intensity and duration of previous ayahuasca use, as well as scores on a personality trait called self-transcendence, a leaning toward spirituality and religiosity and suggested that regular use of psychedelic drugs could result in structural changes in brain areas involved in attentional processes, self-referential thought, and internal mentation. Ayahuasca caused decreased activity in the default mode network, and also decreased connectivity between various components of the default mode network on functional MRI [73].

4.4. Brain Structures Involved in the Ayahuasca Experience

When considered all together, the changes in these particular combinations of brain areas found on imaging fit with the reported experiences of altered awareness, re-experiencing negative memories, and developing new perspectives on problems causing emotional distress. The amygdala, with its increased "utilization rates" [74] of monoamines, brings back the full emotional intensity of the memories. The insula, with its increased blood flow on SPECT imaging [70], could represent the sense of heightened consciousness and increased self-understanding, especially in terms of emotion and relating to others. Many areas of the neocortex show more action, reflected by alterations in perception, cognition, reasoning, and behaviour. The default mode network showed decreased activity on functional MRI, related to alterations in metacognition and self-awareness. The loosening of top-down control over information processing certainly plays a role in the novelty of the experience, as well as the intensified emotional and sensory experience [75]. Ayahuasca-induced changes in many areas of the brain involved in feelings, memories, vision, and consciousness allowed for amplified introspection and problem-solving related to past and current life stressors, and for powerful envisioning and strategizing of solutions for a more hopeful future.

5. PHYSIOLOGIC EFFECTS, SAFETY, AND ADVERSE EFFECTS

One human trial showed that ayahuasca at 1 mg/kg, compared to 20 mg of dextroamphetamine, did not affect subjective sleep quality, initiation or maintenance as measured by polysomnography, decreased REM, and increased slow-wave sleep power [76]. Luke [77] hypothesizes that DMT may play a role in dreaming. DMT depresses startle response in rats [78]. A further experiment showed that low doses (0.25 and 0.5 mg/kg) augmented startle response while a high dose (4.0 mg/kg) depressed it [79]. Another study found that harmine decreased acoustic startle amplitude [80]. A 2002 study assessing sensory and sensorimotor gating showed that with increasing ayahuasca doses there were dose-dependent reductions in P50 suppression [44, 65]. P50 suppression is a test of sensory gating in which paired clicks are heard 50 milliseconds apart, and normally with the second click the amplitude of brain waves (auditory evoked potentials) is much lower, as the brain perceives it as redundant. As an example, in people with schizophrenia, the amplitude is reduced much less than in people without schizophrenia, indicating difficulty with sensory gating. Riba *et al*. [44, 63] also showed no significant effect on sensorimotor gating, as measured by prepulse inhibition of startle response. Vomiting results from increased serotonin (5-HT) stimulating the vagus nerve centrally, and diarrhea may be a result of excessive intestinal stimulation by 5-HT peripherally [47].

5.1. Dependence, Abuse and Tolerance

Morgenstern *et al*. [81] reported that almost no hallucinogen users had difficulty cutting down or controlling use, unlike many other drugs. In a study of rhesus monkeys, Fantegrossi *et al*. [82] found reinforcing effects of the hallucinogens DMT, mescaline, and psilocybin, and suggest that the patterns of self-administration demonstrate weak reinforcing effects, and possibly mixed reinforcing and aversive effects. Ayahuasca does not seem to have the negative psychosocial implications caused by many drugs of abuse [51]. Mixed results were found in studies of drug tolerance in animal studies [83-85] as well as in human studies [3], particularly to the psychoactive effects, which is unique among other known hallucinogens. Callaway *et al*. [86] found that some physical tolerance may develop in humans with regular use. In a study by dos Santos *et al*. [43], acute tolerance failed to develop for any measures aside from growth hormone (GH), which showed decreased release on second administration, as well as a slightly lower response in the systolic blood pressure (SBP) and heart rate (HR). Another study similarly showed tolerance with heart rate, adrenocorticotropic hormone (ACTH) and prolactin [87]. Another study found that there was little to no tolerance with DMT in cats [84].

Beta-carbolines can induce tremor in mice, thought to be due to the interaction of these compounds with tryptamine binding receptors [88]. An experiment by Louis *et al*. [89] suggests we should be cautious with beta-carbolines, as they are found endogenously in higher levels in essential tremor patients, and that harmine and harmane may be tremorigenic. Bouso *et al*. [90] compared two groups of ayahuasca users, one with long term experience and the other with occasional use. The study found that acute use does impair working memory, but having greater prior exposure was associated with less incapacitation during administration, and detrimental effects on cognition were mainly seen in the occasional use group. Those findings suggest there may be neuromodulatory or compensatory effects induced by long term use.

5.2. Psychiatric Symptoms

There is conflicting information on whether endogenous DMT levels are higher in psychotic disorders, and research thus far has been inconclusive [27]. Checkley *et al*. [91] suggested that levels are higher during psychosis but normal after recovery, while Gillin *et al*. [92] argued that DMT levels do not differ significantly between schizophrenics and normal controls, and that DMT does not mimic symptoms of schizophrenia. Another theory proposed that DMT may even serve to suppress psychotic activity, acting as a homeostatic agent [27]. Based on rates of psychotic episodes in the UDV, Gable [3] also concludes that ayahuasca is not a trigger for sustained psychosis. While ayahuasca and other psychedelics could precipate psychosis in predisposed individuals, rates of psychosis in the UDV are comparable to the general population in Brazil [36]. Paterson *et al*. [93] provided a case report of a 42-year-old male without significant psychiatric history who presented with substance-induced psychosis in the context of recent and repeated DMT use as well as long term cannabis use. He improved with quetiapine, divalproex, and hydroxyzine. Warren *et al*. [94] also suggested that recreational DMT use could be a contributor to psychosis. Another case report discussed a man with preexisting bipolar disorder who had a manic episode following ayahuasca consumption [95].

5.3. Endocrine System

Callaway *et al*. [47] reported both GH and prolactin increasing but returning to baseline by 360 minutes, and cortisol increasing to a maximum at 60 minutes, and dipping below basal levels at 360 minutes. GH and prolactin are also influenced by the serotonergic system, so their findings fit with other studies showing an increase in prolactin levels with DMT and other serotonergic drugs such as MDMA, fenfluramine, and citalopram [96, 97].

5.4. Immune System

Dos Santos *et al*. [42] found that relative to placebo, ayahuasca increased total lymphocytes at 1.5 hours, and decreased them at 4.5 hours compared to placebo and to amphetamine, although there was no difference at 24 hours [42]. There were significant decreases in both CD3 and CD4 lymphocytes at 1.5 and 2 hours, no significant changes in CD8 and CD19 lymphocytes, and significant increases in natural killer (NK) cells at 1.5 and 2 hours compared to placebo. No tolerance or sensitization was found with repeat doses [43]. Davydova *et al*. [98] and dos Santos [99] highlighted previous findings and postulated that DMT may activate peripheral 5-HT_{2A} receptors on leukocytes with impacts on cytokine secretion and cell differentiation, and that increased glucocorticoid levels may have modulatory or inhibitory effects on immunity. Amphetamine and MDMA both induce changes similar to ayahuasca, with decreases in CD3 and CD4 lymphocyte levels and increases in NK cell levels [42]. Frecska *et al*. [100] found that DMT caused significantly increased levels of secreted interferon-β and interferon-γ in cultured human NK cells, and suggested that DMT's action at the sigma-1 receptor could be the mechanism for this effect. In an *in vitro* study on human primary monocyte-derived dendritic cells, DMT and 5-MeO-DMT reduced production of several pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and chemokine IL-8, while they increased the secretion of the antiinflammatory cytokine IL-10 [101, 102]. The authors found that these effects were mediated through the sigma-1 receptor, and also noted that both DMT and 5-MeO-DMT impaired the ability of T helper 1 and T helper 17 cells to activate immune responses. House *et al*. [103] noted that harmaline caused a dose-related suppression of CD8 activity, IL-2 and IL-4 production, B cell proliferation, and NK cell function.

5.5. Pupil Size and Body Temperature

DMT causes dose-dependent elevations in pupil size [43, 91]. Callaway *et al*. [47] reported that pupillary diameter increased to a maximum of 4.9 $\pm$ 0.2 mm at 180 minutes, and returned to normal by 360 minutes. Mydriasis has been demonstrated in several IV DMT studies [91, 104]. Mean pupillary light reflex (PLR) amplitude was reduced and PLR latency was increased significantly compared to placebo [42]. A reduced PLR amplitude and increased PLR latency is typically associated with anticholinergics. Two studies found that the serotonin-noradrenaline reuptake inhibitor (SNRI) venlafaxine has the same effect, and they interpreted this as noradrenergic inhibition of parasympathetic transmission on the Edinger-Westphal nucleus, responsible for iris constriction [105, 106].

With respect to body temperature, dos Santos *et al*. [42] compared DMT (at a dose of 1 mg DMT/kg body weight), amphetamine, and placebo, and found that with placebo, body temperature steadily increased over the day, whereas both DMT and amphetamine caused a statistically significant decrease in body temperature during the first hour, followed by a gradual increase, which was larger for amphetamine. Studies involving IV DMT have shown inconsistent results, with one study showing increases and three others showing no change or ambiguous results [46, 104-106].

5.6. Cardiovascular System

In a study of 18 volunteers, Riba *et al*. [13] showed maximum increases in diastolic blood pressure (DBP) of approximately 10 mmHg at 15 minutes, and a maximal systolic BP (SBP) rise of approximately 8 mmHg at 75 minutes following ingestion of ayahuasca containing a 0.85 mg/kg dose of DMT. With respect to heart rate, the maximum increase was approximately 5 beats per minute (BPM) at 60 minutes. Only two of the 18 volunteers had a SBP over 140 (maximum 146) at any point in time, and two volunteers had a DBP over 90 [96]. The same volunteer with the high SBP and DBP had a heart rate of 101 at 60 minutes. Callaway *et al*. [47] found maximal increases in BP at 40 minutes, 11 mmHg for SBP and 9 mmHg for DBP. Heart rate, at its maximal increase, was 7 BPM above baseline at 20 minutes (79 BPM), decreased to a low of 7 BPM below baseline by 120 minutes (65 BPM), then returned toward baseline by 240 minutes. The return to baseline may be due to increasing levels of central 5-HT, mediating cardiac response through the vagus nerve [47]. Another study demonstrated significant increases in HR, SBP, and DBP relative to placebo, with a maximum HR of 150 and SBP of 147 mmHg, while no DBP values went above 90 mmHg [43].

Strassman and Qualls [87] found dose-dependent elevations in HR and BP with IV DMT. They found a larger and more rapid increase than with oral ingestion, reporting that a 0.4 mg/kg IV dose raised HR by approximately 26 BPM at 2 minutes, as well as SBP by 35 mmHg and DBP by 30 mmHg. In the same study, peak heart rates were approximately 150 BPM while some were no higher than 95 BPM. Gable [3] analyzed several studies to compare changes in HR, SBP, and DBP brought on by various psychoactive substances, and concluded that the hemodynamic effects of ayahuasca appear less hazardous than IV DMT, oral alcohol, insufflated cocaine, smoked marijuana, and oral MDMA (Table **1**).

As with any substance that causes acute hemodynamic changes, some adverse cardiac events are possible with the use of ayahuasca [3], although such minimal increases could be attributed to changes in physical activity or other reasons, along the same lines as suggested by Hartley *et al*. [107], who concluded that even just an anxiety-provoking stimulus increases these values more than caffeine; after 14 days of chronic administration, Pitol *et al*. [108] found flattening and stretching of vascular smooth muscle cells, and significant increases in media thickness as well as the ratio of the media thickness to the lumen diameter.

Table 1. Heart rate and blood pressure changes induced by various psychoactive substances (as reported by Gable [3]).

	Heart Rate Increase (BPM)	Systolic Blood Pressure Increase (mmHg)	Diastolic Blood Pressure Increase (mmHg)
DMT	6.4-9.2	8.8-13.8	8.6-10.4
Alcohol	9	-2	1
Caffeine	4	5	5
Cocaine	17	14	14
MDMA	28	25	7

5.7. Toxicity

There have been a few reported cases of poisoning from *P. harmala* seeds. These included a 35-year-old male with abdominal pain, low BP, and convulsions, but this was after ingesting 150 g of *P. harmala* seeds. His symptoms resolved after several hours [109]. It is possible the convulsions could have been related to the inverse agonist effect of some of the beta-carbolines at the benzodiazepine receptor site on the GABA-A receptor [110, 111]. Another case involved a 27-year-old woman who had ingested 50 g of *P. harmala* seeds in a cup of coffee. She presented with hallucinations, bradycardia, nausea, and vomiting, but was discharged several hours later, and laboratory investigation results were all normal [109]. Several similar cases have been reported. In an attempt to investigate the toxicity of ayahuasca, Pic-Taylor *et al*. [112] administered ayahuasca doses 30 and 50 times higher than that typically used in religious rituals to female Wistar rats. While the authors could not calculate an LD_{50} based on their findings, they determined that the lethal dose is higher than 50 times a typical dose used in a religious setting. Pic-Taylor *et al*. [112] also found that the increased serotonergic activation from these high doses led to some neural degeneration, but no permanent alteration in brain structure or number of cells was found.

In our literature search, we found no reports of deaths directly attributable to ayahuasca use. There are a few reported deaths associated with ayahuasca-like herbal preparations, but in these cases it appears coingestion with other substances was to blame; for example, a 25-year-old male had ingested 5-MeO-DMT in addition to beta-carbolines and only trace amounts of DMT, and a 71-year-old diabetic female took a brew containing nicotine as an enema to avoid smoking, and died from nicotine intoxication [3, 113, 114].

A review by dos Santos [115] covers ayahuasca use in pregnancy, and concludes that while some animal studies show toxicity from *in utero* ayahuasca exposure, what little information there is on the topic indicates that there are no serious adverse effects of ayahuasca exposure *in utero* in humans, but more information is needed before its safety in pregnancy is fully understood [66]. Pregnant rats consuming high doses of ayahuasca (10 times the normal human dose) displayed decreased food consumption. The rats displayed decreased weight gain but increased relative liver weight, possibly indicating some hepatotoxicity [116]. As well, these researchers found a dose-response relationship, and fetal effects at 10 times the normal human dose include visceral and skeletal malformations, dilated lateral and third ventricles, along with decreased body weight, thought to represent intrauterine growth restriction (IUGR). A more recent study by Gardner *et al*. [117] discussed congenital malformations in livestock in parts of South America and Mexico, which have long been attributed to ingestion of the *Mimosa tenuiflora* shrub containing N-methyltryptamine (NMT) and DMT. Their findings showed increased rates of cleft palate, scoliosis, and skeletal deformities in rat pups compared to controls when pregnant mothers were fed diets including DMT, NMT, both, or extracts of the *M. tenuiflora* seeds and leaves.

6. PHARMACOLOGY

The DMT in ayahuasca is from the *Psychotria viridis* or *Diplopterys cabrerana* vines, and ranges in concentration from 0.1% to 0.66% of the dry weight [3, 118]. The beta-carbolines come from *Banisteriopsis caapi*. These compounds represent 0.05% to 1.95% of the dry weight, and are much more concentrated in the seeds and roots than in stems and leaves [3]. DMT, a hallucinogen, can be smoked, ingested orally, given IV, or even insufflated [3]. However, when consumed orally, for DMT to exert its effects it is essential that it be consumed mixed with an MAOI to prevent degradation of the DMT by gut and liver MAOs, and to lengthen its action within the CNS [119, 120]. When ayahuasca is consumed, the DMT is taken in combination with beta-carbolines which act as reversible inhibitors of monoamine oxidase A (MAO-A), protecting the DMT from degradation [121].

In a review on ayahuasca, Gable [3] looked at previous data on the composition of one serving of various studies' brews, and found a range of 8.8 mg to 42 mg for DMT, 17 mg to 280 mg harmine, 4.6 mg to 28 mg harmaline, and 4.2 to 150 mg for tetrahydroharmine; these wide variations are attributed to different composition of the plants as well as differences in preparation methods. A recent study on ayahuasca samples from Brazilian religious groups found DMT concentrations ranging from 0.17-1.14 g/L [120], which, assuming an average serving size similar to previous studies being around 150 mL, would give a dose ranging from 25.5 to 171 mg of DMT per serving.

Chemical profiling of the aqueous extract from *B. caapi* stems revealed a number of substances [119-123], some of which had not yet been identified in *B. caapi*. Wang *et al*. [124] found two new beta-carboline alkaloidal glycosides

(Banisteride A and B) and their acetates, four known beta-carbolines (harmine, harmaline, tetrahydroharmine, and harmol), a new beta-carboline (tetrahydronorharmine), two proanthocyanides [(-)-epicatechin and (-)-procyanidin B2)] and their acetates, a new dissacharide (β-d-fructofuranosyl-(2→5)-fructopyranose) and its acetate, known saccharose and acetate, and β-D-glucose. Several studies found similar chemical profiles. Two quinazoline alkaloids, peganine and deoxypeganine, have also been isolated in a *P. harmala* seed infusion [125].

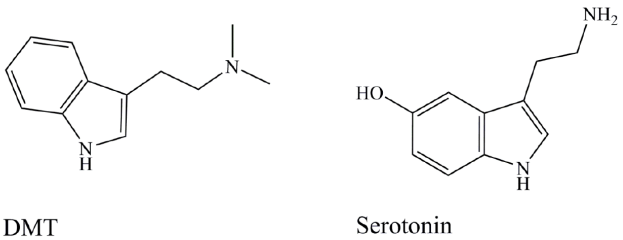
The toxic dose of ayahuasca would be approximately 7.8 litres for a 75 kg person. Given its highly unpleasant taste, it is unlikely anyone would ever reach this dose. In addition, vomiting and diarrhea occur long before this limit is reached [5].

6.1. DMT

DMT (Fig. **1**) is a serotonin-like hallucinogen structurally resembling other indolealkylamines, including melatonin and psychedelic tryptamines such as psilocybin, and is known mostly for its activity as a 5-HT_{2A} receptor agonist [15, 126]. DMT is found in fungi, marine sponges, tunicates, frogs, legumes, and grasses [27] and has been reported to be formed endogenously in human and rat brains [127] as well as to be found in human urine, blood, and CSF. DMT has affinity for 5-$HT_{1A/1B/1D/2A/2B/2C/6/7}$ receptors, with proven partial agonist activity at the 5-$HT_{1A/2A/2C}$ receptors [80, 118, 128, 129]. Carbonaro *et al*. [130] proposed that the mGluR2 glutamate receptors may have some involvement in DMT's hallucinogenic effect. Current understanding is that psychedelic effects are mediated mainly by 5-$HT_{2A/2C}$ receptors. 5-HT_{2A} receptor activation has also been associated with sympathetic activation which may explain some of the physiologic effects of ayahuasca administration [87, 131].

DMT activity was demonstrated at the rat trace amine-associated receptor 1 (TAAR1) by Bunzow *et al*. [132], where tryptamine is also thought to act as a neurotransmitter [27]. Premont *et al*. [133] suggested that DMT may function endogenously as part of this system, and proposed that trace levels of endogenous DMT act to produce a calmer, more relaxed mental state and suppress psychosis.

DMT binds to sigma-1 receptors with a moderate affinity, and Fontanilla *et al*. [128] proposed that DMT is likely to serve as an endogenous sigma-1 receptor ligand. The function of this receptor is not well understood, although it is found in lung, prostate, colon, ovaries, breasts, and liver, and is most concentrated in the brain. This receptor may play a role in depression, anxiety, and cancer [134]. Sigma-1 receptors are molecular chaperones situated on the mitonchondria-associated endoplasmic reticulum membrane, although when stimulated with high concentrations of ligands, may translocate to the cell's plasma membrane, where they inhibit several ion channels. DMT has also shown affinity for α1- and α2-adrenergic receptors as well as the dopamine D_1 receptor [135].



DMT Serotonin

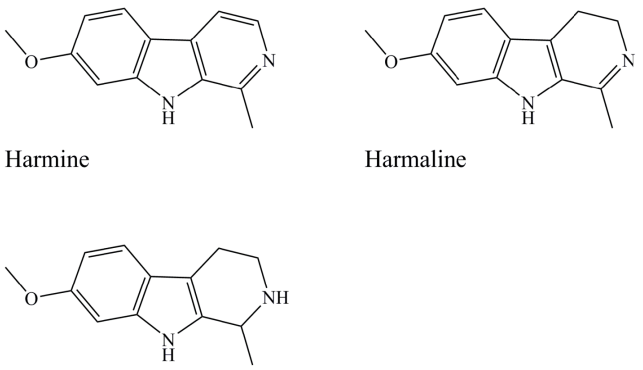
Fig. (1). Structures of DMT and serotonin (5-HT).

6.2. beta-Carbolines Harmine, Harmaline, and Tetrahydroharmine

Beta-carbolines (Fig. **2**) are tricyclic indole alkaloids resembling tryptamines [10]. 6-Methoxy-tetrahydro-β-carboline has been found in the human pineal gland [136]. Several beta-carbolines are found in the *B. caapi* vine, including harmine, harmaline, and tetrahydroharmine. The first two act as selective and reversible monoamine oxidase A inhibitors (MAO-AIs), while tetrahydroharmine acts as a weak serotonin reuptake inhibitor without any MAO-AI action [47]. Beta-carbolines are found naturally in wheat, rice, corn, barley and throughout different body tissues [89]. They elicit their effects through several mechanisms.

Beta-carbolines without DMT have been shown to produce psychological and physiologic effects, as in a case of intoxication following *Paganum harmala* seed extract [137]. The effects, including nausea, vomiting [130], hallucinations, ataxia, confusion, and agitation were attributed to CNS stimulation by MAOI activity as well as the serotonin reuptake inhibition by tetrahydroharmine. Frison *et al*. [137] suggested that the hallucinogenic effects could be a result of the affinity of harmine and harmaline for 5-HT receptors. Beta-carbolines from the *B. caapi* vine taken without DMT are used by the Piaroa of Southern Venezuala. Piaroa shamans and people who use *B. caapi* describe enhanced empathy, stimulant-like effects, and increased visual acuity, and they also use it as a hunting aid [138, 139].

The main mechanisms of action proposed for beta-carbolines include the MAO-A inhibitory activity, dopamine efflux, and affinity for the 5-HT_{2A} binding site [140]. Other less studied mechanisms include dopamine transporter (DAT) inhibition at high concentrations in particular of beta-carboline compounds [141], harmine as a specific tyrosine-phosphorylation-regulated kinase 1A (DYRK1A) inhibitor [142], and affinity for the imidazoline (I_2) binding site [143].



Harmine Harmaline

Tetrahydroharmine

Fig. (2). Structures of harmine, harmaline and tetrahydroharmine.

Harmine has also been found to regulate expression of the peroxisome proliferator-activated receptor gamma (PPAR-ɣ, also known as the glitazone receptor) and shows some antitrypanosomal activity [144]. Harmine upregulates the glutamate transporter (GLT-1, also called excitatory amino acid transporter 2, or EAAT2), the primary mechanism for inactivating synaptic glutamate [145]. Harmane, harmine, and norharmane have also been found to act as inverse agonists at the benzodiazepine binding site (between the α and ɣ subunits) of the GABA-A receptor [110]. Another study showed that 4 beta-carbolines (1,2,3,4-tetrahydronorharmane, norharmane, harmane, and 6-methoxyharmalan) act as competitive antagonists at the glycine receptor ligand binding site, leading to inhibition at the glycine receptor [111].

A recent study on neurotransmitter concentrations in the amygdala and hippocampus of rats killed 40 minutes after administration of an ayahuasca infusion reported that ayahuasca reduced levels of glycine and GABA in rat amygdala. This is suggestive of an increased release of these neurotransmitters in the amygdala, leading to greater inhibition, while in the hippocampus, it increased GABA levels, suggestive of a decrease in GABA release and excitation at this structure [74]. These opposite effects on the level of inhibitory neurotransmission in these two limbic structures may provide some explanation into the behavioural effects of ayahuasca, due to the importance of these structures in neural pathways involved in memory, learning, and emotion.

Harmine and harmaline affect dopamine pathways both by causing a significant increase in DA release from striatal cells and by acting as reversible MAO-A inhibitors. A study on the nucleus accumbens of rats [146] found that harmine increases electrically evoked DA efflux in the nucleus accumbens shell. Brierley & Davidson [140] proposed that, given harmine has some affinity for the 5-$HT_{2A/2C}$ receptors but not for the dopamine receptor [147], this effect has a 5-HT_{2A}-mediated mechanism. Grella *et al*. [148] also found that certain beta-carbolines bind at the 5-HT_2 receptor. In another experiment in rat striatum, dose dependent decreases in the levels of DA metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were also seen, as well as decreases in levels of the serotonin breakdown product 5-hydroxyindoleacetic acid (5-HIAA), though not to the same extent as with the dopamine metabolites [149]. These effects are additive when mixtures of various beta-carbolines are used [123]. The dopamine transporter serves to actively shift dopamine from the synapse into the presynaptic neuron, acting as the primary mechanism for regulating dopaminergic activity [150]. Harmine was found to inhibit DA uptake through the DAT in rats. Dopaminergic neurotransmission is primarily modulated through regulation of the dopamine transporters, which act to shuttle extracellular dopamine back into the neurons. Harmine acts a potent ATP-competitive inhibitor of the DYRK1A enzyme, which inhibits synaptic vesicle endocytosis and DAT membrane trafficking, possibly by phosphorylating vesicle proteins taking part in clathrin-mediated endocytosis that serves to regulate DAT trafficking [151, 152]. DYRK1A overexpression has been implicated in defective neural development in Down Syndrome, and the protein has also been implicated in amyloid pathology as well as in tau protein phosphorylation (at serine 262/356/396) in both Down Syndrome and Alzheimer's disease [153].

6.3. Long Term Neurochemical Modulation

Ayahuasca was found to upregulate platelet serotonin transporters [86]. Disorders that have been suggested to be associated with low serotonin transporter densities include alcoholism (particularly with violent tendencies), suicidal behaviour, and severe depression [10]. The glutamate transporter GLT-1/EAAT2 is the main mechanism for extracellular glutamate uptake in the brain, and dysfunction may lead to excessive synaptic glutamate and excitotoxicity. Harmine has been found to activate the GLT-1 gene promoter, leading to increased gene expression and greater extracellular glutamate uptake [145]. Certain beta-carbolines have been found to bind at imidazoline binding sites, including harmine and harmaline found in ayahuasca [143]. Husbands *et al*. [143] suggested that the imidazoline type 2 (I_2) receptors may play a role in the hallucinogenic nature of ayahuasca given that harmine and harmaline have much higher affinities for the I_2 receptor than the 5-HT_{2A} receptor. Harmine also increases superoxide dismutase and catalase activity, and these antioxidant effects may have relevance in depression and several neurodegenerative disorders [154].

6.4. Pharmacokinetics

Callaway [155] studied slow versus fast metabolizers and cytochrome P4502D6 (CYP2D6) variations in humans. The main isozymes involved in O-demethylation of harmaline into harmalol are CYP1A1, CYP1A2, and CYP2D6, while CYP1A1, CYP1A2, CYP2C9, CYP2C19, and CYP2D6 catalyze the O-methylation of harmine into harmol. These metabolites are then excreted as glucuronates and sulphates [156, 157]. Harmane may break down into harmine [89]. Only one case report attempted to quantify and compare concentrations and amounts of harmine and harmaline in an ayahuasca infusion and urine; however, it was difficult to draw any conclusions given the amount of uncertainty surrounding the preparation and ingestion [137].

Compared to DMT from ayahuasca, smoked, IV and insufflated DMT all have a very rapid onset of activity, with peak cognitive effects lasting 3-10 minutes and episodes 5-15 minutes. Ayahuasca produced a cognitive peak between 60 and 120 minutes and effects lasting approximately four hours [10]. Recreational DMT users describe the experience as short, intense, and pleasurable [158]. In addition, ayahuasca has somatic effects that appear approximately 20 minutes after consumption, including nausea, tingling, and increased body temperature [3].

With respect to plasma peak levels, Callaway *et al*. [47] showed an average time to reach maximum concentration (T_{max}) of 107.5 $\pm$ 32.5 minutes with 15 volunteers, and the half life ($T_{1/2}$) was 259 minutes. dos Santos *et al*. [42] noted a median T_{max} of 1.8 hours, with a range of 1-4.5 hours. Riba *et al*. [13] found a median T_{max} for orally consumed DMT of 1.5 hours for both high and low doses (0.6 mg/kg and 0.85 mg/kg), but showed a correlation between higher doses and a larger T_{max}. This aligns with the finding of a cognitive peak

between 60 and 120 minutes reported by Gable [3], as well as peaking along a similar timeline as EEG activity [65]. The threshold for hallucinogenic effects for DMT was 0.2 mg/kg by IV. IV DMT administration also differs in that the effects come on more rapidly and last for a shorter time, displaying peak blood levels and subjective effects within 2 minutes; both were neglible at 30 minutes [3, 87]. Gable [3] noted a median lethal dose (LD_{50}) for DMT of 47 mg/kg intraperitoneally and 32 mg/kg IV in mice, which is similar to the IV LD_{50} in rodents for other compounds resembling DMT structurally (psilocin, psilocybin, bufotenin, 5-MeO-DMT). In comparing toxicities of various psychoactive drugs, ayahuasca has a safety margin similar to those of codeine, mescaline, and methadone, with the lethal dose being approximately 20 times the usual effective dose [159]. Lanaro *et al*. [160] discussed differences between ritual oral ingestion of ayahuasca and recreational smoked DMT and noted that with smoked DMT the bioavailability and risk of overdose are much higher.

DMT is catabolised mainly by oxidative deamination as well as N-oxidation and N-demethylation [27]. Metabolic studies showed indole-3-acetic acid (IAA) and indole-3-aceturic acid (IAA conjugated with glycine) as the main urinary metabolites of DMT in rats [161]. Riba *et al*. [162] described urinary metabolites of oral and smoked DMT. Without the beta-carbolines found in ayahuasca, after oral ingestion of DMT, no psychoactive effects occurred; 97% of recovered compound was IAA, an MAO-dependent metabolite, and 3% was DMT-N-oxide (DMT-NO). DMT-NO does not appear to be a substrate for MAO. With smoked DMT, unmetabolized DMT and DMT-NO accounted for 10% and 28%, respectively, of recovered compounds, while IAA accounted for 63%. N-methyltryptamine (NMT), 2-methyl-1,2,3,4-tetrahydro-beta-carboline (2-MTHBC) and 1,2,3,4-tetrahydro-beta-carboline (THBC) have also been identified as minor metabolites of DMT [27].

A study by Callaway *et al*. [47] found T_{max} values (minutes) for DMT of 107.5 ± 32.5, for harmine 102.0 ± 58.3, for harmaline 145.0 ± 66.9, and for tetrahydroharmine (THH) 174.0 ± 39.6 after an ayahuasca infusion. Riba *et al*. [13] reported that THH peaked later in the serum than DMT and harmaline. Compared to low dose, high dose ayahuasca seemed to show slightly longer T_{max} values for these constituents. They were unable to obtain sufficient measurable plasma levels for harmine, but had measurable levels of harmol (metabolite of harmine) with plasma concentration peaks at 1.5 and 2 hours after low and high doses. They were able to measure harmaline, and T_{max} was at 1.5 and 2 hours for the low and high doses. In general, the studies by Riba *et al*. [13] and Callaway *et al*. [47] (Table **2**) show a trend of T_{max} increasing from DMT through harmaline to THH. In terms of toxicity, Gable [3] found a median lethal dose/LD_{50} of 2 g/kg *P. harmala* seed beta-carboline admixture in rats.

7. DRUG-DRUG INTERACTIONS

There is a possibility that any substances, including beta-carbolines, that act as MAO-AIs can produce serotonin syndrome [179]. McKenna [10] suggested that DMT and the beta-carbolines in ayahuasca, when combined with an SSRI antidepressant could cause serotonin syndrome. Callaway & Grob [163] also report a case of serotonin syndrome in a patient using the SSRI fluoxetine in conjunction with ayahuasca. The irreversible, nonselective MAOIs phenelzine and tranylcypromine are associated with serotonin syndrome, and there are also cases with opiates, analgesics, tricyclic antidepressants (TCAs), SSRIs, and antimigraine drugs, and it is suggested that those who have recently used any ginseng, St. John's wort, dextromethorphan, or MDMA should be cautious [3]. A chart of potential interactions exists on the harm reduction organization TripSit's website (TripSit.me). Balikova [24] reported on an incident of 30 people who ingested a brew containing harmine, atropine, and scopolamine in a meditation session, and found tachycardia, amnesia, hallucinations, hyperthermia, hypotension, mydriasis, collapse, coma, and even respiratory depression requiring mechanical ventilation. A synergistic effect was found with beta-carbolines in combination with atropine and scopolamine; the ingested doses of the three substances were all 8 to 13 times less than estimated lethal doses [3].

Harmine, harmol, and harmane have been found to be noncompetitive inhibitors of CYP3A4; they are also both substrates and inhibitors of CYP2D6. Harmaline, harmine and harmol showed competitive inhibition of CYP2D6 [164]. With two major CYP enzymes inhibited, users should be cautious of drug interactions. As well, genetic polymorphisms can affect the efficacy of these enzymes.

8. POTENTIAL PSYCHIATRIC USES

8.1. Addictions

Ayahuasca appears to be beneficial in treatment of addictions, and when used appropriately does not appear to carry risks of abuse or dependence [81]. Ayahuasca may enable sustained abstinence from alcohol, barbiturates, sedatives,

Table 2. T_{max} findings for DMT, harmine, harmol, and harmaline, and THH in various studies.

		DMT	Harmine	Harmol (Metabolite of Harmine)	Harmaline	THH
Callaway *et al*. [47]	average T_{max} in minutes	107.5 ± 32.5	102.0 ± 58.3		145.0 ± 66.9	174.0 ± 39.6
Riba *et al*. [13]	median T_{max} in hours at low dose	1.5 (1-2.5)		1.5 (1-2.5)	1.5 (1-3)	2.5 (1.5-3)
Riba *et al*. [13]	median T_{max} in hours at high dose	1.5 (1-4)		2 (1-3)	2 (1-4)	3 (1.5-6)
dos Santos *et al*. [42]	median T_{max} in hours	1.8 (1-4.5)				

cocaine, amphetamines, and solvents, though most continue to use marijuana [51]. Compared to matched controls, regular participants in Brazilian ayahuasca church ceremonies scored significantly lower on the Addictions Severity Index subscales of Alcohol Use and Psychiatric Status, although the authors noted that it is hard to separate whether these effects are from the ayahuasca, involvement in a supportive community, or both [51]. Barbosa *et al*. [17] suggest that based on their findings, administration of hallucinogens in both clinical settings and religious settings can provide benefits.

Any drug that affects dopamine has potential for abuse, and although harmine does, it does not cause dependence. Ayahuasca does not show activation in reward-related regions of the striatum or ventral-tegmental area on SPECT imaging [51,70], and only causes increased blood flow in the frontal and paralimbic areas.

Liester & Prickett [165] suggest 4 hypotheses to explain ayahuasca's proposed antiaddictive properties:

1. Ayahuasca reduces brain dopamine levels or activity in the mesolimbic dopamine pathway, decreasing the reward associated with an addictive substance. DMT is a known 5-HT_{2A} receptor agonist and 5-HT_{2A} receptor agonism is known to inhibit dopamine release in the mesolimbic, nigrostriatal, and mesocortical pathways. Reduced brain dopamine also fits with elevated prolactin levels with ayahuasca use [4]. The opposite is also true as illustrated by atypical antipsychotics, which have 5-HT_{2A} receptor antagonist activity and exhibit reduced dopamine blockade (70-80% blockade) compared to typical antipsychotics (90%) which have little action at serotonin receptors [166].

2. Reduced dopamine in reward pathways impairs the synaptic plasticity involved in addiction development and maintenance.

3. The introspection, self-realizations, and healing of past traumas afforded by an ayahuasca experience offer better understanding of consequences and improved decision-making, empowering the individual to abstain.

4. Ayahuasca facilitates transcendent experiences; the authors give the example of Bill Wilson, founder of Alcoholics Anonymous, having such an experience (not ayahuasca induced) and being able to give up alcohol.

8.2. Cocaine Dependence

A study by Glick *et al*. [167] reported that harmaline led to significantly reduced cocaine and morphine self-administration in rats. While cocaine increases dopamine efflux and reuptake inhibition in both the shell and core of the nucleus accumbens, harmine only augments efflux in the shell of the nucleus accumbens [140, 147], perhaps demonstrating one mechanism of harmine that is similar to cocaine that can be useful in treatment and has far less addictive potential. As mentioned above, a Canadian study by Thomas *et al*. [35] showed that ayahuasca holds promise as a potential treatment for cocaine dependence, with a statistically significant reduction in use (by self-report) that is greater than the reduction in either tobacco or alcohol use.

8.3. Alcoholism

Halpern [168] touched on promising past research involving LSD in the treatment of alcoholism and anecdotal evidence of peyote containing mescaline used in the Native American Church being potentially useful in treating drug dependence and alcohol addiction, and suggested it is time to start studying hallucinogens again. As mentioned previously, Doering-Silveira *et al*. [169] found that adolescents from a Brazilian ayahuasca-using church had less recent alcohol use (32.5%) compared to adolescents who had never used ayahuasca (65.1%). Oliveira-Lima *et al*. [170] showed that in mice, ayahuasca inhibited some of the early behaviours that were associated with developing alcohol addiction.

8.4. Pain Treatment and Opioid Dependence

Beta-carbolines may prove useful in treating opioid addiction. Harmine and harmaline act as imidazoline type 2 receptor agonists I_2 [143]. Harmane and harmine have both been reported to reduce the symptoms of morphine withdrawal [171]. Miralles *et al*. [172] assessed the affinity of various beta-carbolines for the I_2 binding site in brain and liver and also found that norharmane prevents the stimulatory effects of opioid withdrawal as measured by withdrawal symptom severity, and attenuated L-3,4-dihydroxyphenylalanine (L-dopa) synthesis normally associated with withdrawal.

8.5. Depression

Osorio *et al*. [173], in an open label trial in an inpatient psychiatric unit, found that a single dose of ayahuasca has rapid acting anxiolytic and antidepressant effects in patients with recurrent depression. dos Santos *et al*. [174] reviewed several clinical trials on ayahuasca, psilocybin, LSD, and their effects and concluded that all these drugs could be beneficial in treatment of depression (especially in treatment-resistant subjects), as well as anxiety and alcohol and tobacco dependence. The results also seemed to confirm that both the DMT and the beta-carbolines in ayahuasca show promise as effective depression and anxiety treatments. They highlighted findings that 5-HT_{1A} receptor agonists have shown antidepressive and anxiolytic effects in both humans and animals, and 5-$HT_{2A/2C}$ agonists had antidepressive and anxiolytic effects in animal studies. In addition, 5-$HT_{1A/2A/2C}$ receptor agonists have shown anti-inflammatory properties, and there is growing evidence that inflammation is another process implicated in the pathogenesis of anxiety and depression [175].

Several studies of harmine have shown an antidepressant effect [176-180]. One known mechanism through which harmine and harmaline may exert an antidepressant effect is reversible inhibition of MAO-A [181], resulting in increased neurotransmission. Their reversibility for MAO-A inhibition makes them safer than the traditional nonselective, irreversible MAOIs [10]. Fortunato *et al*. [178, 179] have conducted several animal studies assessing the antidepressant effect of harmine. Using the forced swim test, it was shown that the animals treated with harmine had decreased immobility and more swimming and climbing, and they had increased levels of brain-derived neurotrophic factor (BDNF) which has an

antidepressant effect in the brain [177-180]. Harmine was also able to reverse the anhedonic effects of the chronic mild stress test [179]. Harmine acts to decrease synaptic glutamate *via* increased GLT-1/EAAT2 expression and subsequently increasing glutamate transport [145].

DMT activates sigma-1 receptors. Other antidepressants, though not all, of the SSRI, MAOI and TCA classes have been found to do so as well. These receptors are found throughout the nervous system, and are concentrated in the hippocampus, frontal cortex, and olfactory bulb, consistent with a possible role in depression [182]. Past experiments have shown an antidepressant-like effect in mice administered sigma-1 receptor agonists [183] and attenuation of these effects with sigma receptor antagonists [181]. Agonists of the sigma receptor are being studied as potential antidepressant drugs [182]. More work into the functions of sigma receptors and their role in depression treatment is needed. A possible connection lies in the inhibitory effect of DMT on the NMDA receptor through sigma receptor activation [134].

Both I_1 and I_2 imidazoline receptors have been associated with the pathology of depression. I_1 sites are decreased in brains of depressed suicide victims, notably in the hippocampus and prefrontal cortex [184]. I_1 binding sites are found throughout the human brain, and the highest density areas include in the striatum, pallidum, hippocampus, amygdala, and substantia nigra [185]. I_1 receptors are thought to be involved in the central inhibition of sympathetic outflow, which can be altered in depression and hypertension [186]. Interestingly, the number of I_1 binding sites are reported to be increased on platelets of patients experiencing depression and premenstrual dysphoric disorder. This effect was highly correlated with severity of symptoms, but there was a consistent return to normal levels following treatment with fluoxetine, citalopram, bupropion, desipramine, clomipramine, imipramine, and lithium, even though several of these drugs act through different mechanisms, which suggests platelet I_1 density could be used as a possible biological marker of depression [186]. Halaris & Piletz [186] also described an unpublished finding that in nondepressed patients, desipramine failed to produce the same effect. Therefore, platelet I_1 sites could have potential as a biological marker of depression, as well as a measure of response to treatment. A downregulation of I_2 binding sites has been found in frontal cortices and hippocampi of depressed humans postmortem. Harmine and harmaline have high affinity for the I_2 binding site in rat brains [188]. In terms of clinical use, the selective I_2 ligand BU224 showed antidepressant-like activity in rats and increased 5-HT levels in the frontal cortex and hypothalamus [185]. Antidepressant treatment caused upregulation of I_2 sites in rat brains [187]. Most I_2 selective ligands have been found to be allosteric inhibitors of both MAO-A and MAO-B [188].

Evidence is now suggesting that reactive oxygen species may be involved in the pathogenesis of depression and anxiety [189]. Harmine has shown to be of benefit as it increased levels of both superoxide dismutase and catalase enzymes, and attenuated oxidative stress parameters of lipid and protein oxidation in rat brain hippocampus, a structure involved in mood regulation [154].

8.6. Anxiety

Jacob & Presti [190] suggested that DMT action at a trace amine receptor may produce an anxiolytic effect. Anxiety, like depression, is another disorder which has been linked to oxidative stress [189]. Sarris *et al*. [191] highlight ayahuasca as a treatment of potential use in their review of plant based medicines for anxiety. A double blind study showed a statistically significant reduction of hopelessness and panic-like parameters using standardized questionnaires, the Beck Hopelessness Scale and the Revised Anxiety Sensitivity Index upon acute ayahuasca ingestion [192]. Furthermore, it has been suggested that DMT acts in a manner similar to serotonin, and 5-HT_2 receptor activation has been shown to alleviate panic symptoms [193]. It is important to note that some beta-carbolines may have a possible anxiogenic effect, given their inverse agonist effect at the benzodiazepine receptor site of the GABA-A receptor [110, 111].

8.7. Psychotherapy

There are many reported psychotherapeutic benefits of ayahuasca, however most studies stress that this is only when it is used in specific settings [10]. Like LSD in the 1950s, ayahuasca is now being considered as a tool to facilitate psychotherapy, by dissolving the ego, promoting introspection, and aiding in processes of self-analysis [194]. Barbosa *et al*. [11] suggested that hallucinogens may also act to facilitate association and memory processing. However, regulations governing the use of psychoactive substances often limit the ability to undertake scientific investigations of such novel approaches.

CONCLUSION

Centuries of shamanic wisdom have demonstrated potential therapeutic uses for ayahuasca. Currently, we do not have highly successful treatments for addictions, and it seems shortsighted not to remain open to possibilities beyond our standard repertoire of treatment modalities. Certainly, there are challenges in studying substances situated at the fringes of both science and mainstream culture, and legal obstacles can play a role in delaying scientific advancement. To some, studying hallucinogens may seem taboo, but studying the specific effects of psychoactive substances such as ayahuasca has the potential to yield useful information in the treatment of many psychiatric and medical conditions, as emphasized in recent years by several researchers [1, 29, 30, 36, 195-197]. We caution, however, that such studies should be done by recognized, credible researchers and that such studies must include a comprehensive recording of side effects as well as beneficial effects. These studies should be fully registered with the appropriate global clinical databases (*e.g*. NIH Clinical Trials Database) and the peer-reviewed papers should be open access. Many of the studies conducted to date with ayahuasca have been small and lacked appropriate controls. Although the adverse effects in humans have often been reported to be relatively mild [7], people must not take its use lightly, and should be aware of the unpleasant effects associated with use of ayahuasca and of potential adverse effects described in several references in this review [3, 23, 62, 135, 164, 197]. Consistency of the dose and makeup

of the ayahuasca brew are serious matters to be considered, as are potential interactions with other drugs the subject is taking [156, 157].

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Halpern, J.H.; Sherwood, A.R.; Passie, T.; Blackwell, K.C.; Ruttenber, A.J. Evidence of health and safety in American members of a religion who use a hallucinogenic sacrament. *Med. Sci. Monit.,* **2008**, *14*(8), SR15-SR22. [PMID: 18668010]

[2] Kjellgren, A.; Eriksson, A.; Norlander, T. Experiences of encounters with ayahuasca--"the vine of the soul". *J. Psychoactive Drugs,* **2009**, *41*(4), 309-315. [http://dx.doi.org/10.1080/02791072.2009.10399767] [PMID: 20235436]

[3] Gable, R.S. Risk assessment of ritual use of oral N,N-dimethyltryptamine (DMT) and harmala alkaloids *Addiction*; M.J, Winkelman; T.B, Roberts, Eds.; Psychedelic Medicine (Vol 2): New evidence for hallucinogenic substances as treatments, **2007**, *102*, (1), 24-34.

[4] 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. Pharmacokinetics of Hoasca alkaloids in healthy humans. *J. Ethnopharmacol.,* **1999**, *65*(3), 243-256. [http://dx.doi.org/10.1016/S0378-8741(98)00168-8] [PMID: 10404423]

[5] Mabit, J. Ayahuasca in the treatment of addictions. Psychedelic Medicine (Vol 2): New Evidence for Hallucinogenic Substances as Treatments, **2007**, 87. M.J, Winkelman; T.B, Roberts Praeger Publishers Westport, CT(105).

[6] Dobkin de Rios, M. Ayahuasca--the healing vine. *Int. J. Soc. Psychiatry,* **1971**, *17*(4), 256-269. [http://dx.doi.org/10.1177/002076407101700402] [PMID: 5145130]

[7] Dos Santos, R.G.; Osório, F.L.; Crippa, J.A.S.; Hallak, J.E. Antidepressive and anxiolytic effects of ayahuasca: a systematic literature review of animal and human studies. *Br. J. Psychiatry,* **2016**, *38*(1), 65-72. [http://dx.doi.org/10.1590/1516-4446-2015-1701] [PMID: 27111702]

[8] Grob, C.S.; McKenna, D.J.; Callaway, J.C.; Brito, G.S.; Neves, E.S.; Oberlaender, G.; Saide, O.L.; Labigalini, E.; Tacla, C.; Miranda, C.T.; Strassman, R.J.; Boone, K.B. Human psychopharmacology of hoasca, a plant hallucinogen used in ritual context in Brazil. *J. Nerv. Ment. Dis.,* **1996**, *184*(2), 86-94. [http://dx.doi.org/10.1097/00005053-199602000-00004] [PMID: 8596116]

[9] Desmarchelier, C.; Gurni, A.; Ciccia, G.; Giulietti, A.M. Ritual and medicinal plants of the Ese'ejas of the Amazonian rainforest (Madre de Dios, Perú). *J. Ethnopharmacol.,* **1996**, *52*(1), 45-51. [http://dx.doi.org/10.1016/0378-8741(96)01390-6] [PMID: 8733119]

[10] McKenna, D.J. The healing vine: Ayahuasca as medicine in the 21st century. Psychedelic Medicine: New Evidence for Hallucinogenic Substances as Treatments; Winkelman, M.J.; Roberts, T.B., Eds.; Praeger Publishers, **2007**, Vol. 1, pp. 21-44.

[11] Barbosa, P.C.R.; Giglio, J.S.; Dalgalarrondo, P. Altered states of consciousness and short-term psychological after-effects induced by the first time ritual use of ayahuasca in an urban context in Brazil. *J. Psychoactive Drugs,* **2005**, *37*(2), 193-201. [http://dx.doi.org/10.1080/02791072.2005.10399801] [PMID: 16149333]

[12] Labate, B.C. Consumption of ayahuasca by children and pregnant women: medical controversies and religious perspectives. *J. Psychoactive Drugs,* **2011**, *43*(1), 27-35. [http://dx.doi.org/10.1080/02791072.2011.566498] [PMID: 21615005]

[13] Riba, J.; Valle, M.; Urbano, G.; Yritia, M.; Morte, A.; Barbanoj, M.J. Human pharmacology of ayahuasca: subjective and cardiovascular effects, monoamine metabolite excretion, and pharmacokinetics. *J. Pharmacol. Exp. Ther.,* **2003**, *306*(1), 73-83. [http://dx.doi.org/10.1124/jpet.103.049882] [PMID: 12660312]

[14] Lemlij, M. Primitive group treatment. *Psychiatr. Clin. (Basel),* **1978**, *11*(1), 10-14. [PMID: 704949]

[15] Cakic, V.; Potkonyak, J.; Marshall, A. Dimethyltryptamine (DMT): subjective effects and patterns of use among Australian recreational users. *Drug Alcohol Depend.,* **2010**, *111*(1-2), 30-37. [http://dx.doi.org/10.1016/j.drugalcdep.2010.03.015] [PMID: 20570058]

[16] Cardenas, A.V.; Gomez, A.P. Urban use of yaje (ayahuasca) in Colombia. *Adicciones,* **2004**, *16*, 323-334.

[17] Barbosa, P.C.R.; Cazorla, I.M.; Giglio, J.S.; Strassman, R. A six-month prospective evaluation of personality traits, psychiatric symptoms and quality of life in ayahuasca-naïve subjects. *J. Psychoactive Drugs,* **2009**, *41*(3), 205-212. [http://dx.doi.org/10.1080/02791072.2009.10400530] [PMID: 19999673]

[18] Fiedler, L.; Jungaberle, H.; Verres, R. Motives for the consumption of psychoactive substances demonstrated in the example of the use of ayahuasca in the Santo Daime community. *Zeitschr Fur Medizin Psychol.,* **2011**, *20*, 137-144.

[19] Holman, C. Surfing for a shaman: Analyzing an ayahuasca website. *Ann. Tour. Res.,* **2011**, *38*(1), 90-109. [http://dx.doi.org/10.1016/j.annals.2010.05.005]

[20] Fotiou, E. From medicine men to day trippers: Shamanic tourism in Iquitos, Peru. Dissertation Abstracts Int Section A: Humanities and *Social .Sci.*, **2011**, *72*(1-A), 256.

[21] Winkelman, M. Drug tourism or spiritual healing? Ayahuasca seekers in Amazonia. *J. Psychoactive Drugs,* **2005**, *37*(2), 209-218. [http://dx.doi.org/10.1080/02791072.2005.10399803] [PMID: 16149335]

[22] Arrévalo, G. Interview with Guillermo Arrévalo, a Shipibo urban shaman, by Roger Rumrrill. Interview by Roger Rumrrill. *J. Psychoactive Drugs,* **2005**, *37*(2), 203-207. [http://dx.doi.org/10.1080/02791072.2005.10399802] [PMID: 16149334]

[23] Kavenska, V.; Simonova, H. Ayahuasca tourism: participants in shamanic rituals and their personality styles, motivation, benefits and risks. *J. Psychoactive Drugs, 47*, 351-359. B2015B.

[24] Balíková, M. Collective poisoning with hallucinogenous herbal tea. *Forensic Sci. Int.,* **2002**, *128*(1-2), 50-52. [http://dx.doi.org/10.1016/S0379-0738(02)00162-7] [PMID: 12208022]

[25] Shulgin, A.T.; Shulgin, A.; Perrine, D.M. Tihkal: the continuation **1997**.

[26] Labate, B.C.; Cavnar, C. The expansion of the field of research on ayahuasca: some reflections about the ayahuasca track at the 2010 MAPS "Psychedelic Science in the 21st Century" conference. *Int. J. Drug Policy,* **2011**, *22*(2), 174-178. [http://dx.doi.org/10.1016/j.drugpo.2010.09.002] [PMID: 21051213]

[27] Araújo, A.M.; Carvalho, F.; Bastos, Mde.L.; Guedes de Pinho, P.; Carvalho, M. The hallucinogenic world of tryptamines: an updated review. *Arch. Toxicol.,* **2015**, *89*(8), 1151-1173. [http://dx.doi.org/10.1007/s00204-015-1513-x] [PMID: 25877327]

[28] Kowalczuk, A.P.; Łozak, A.; Bachliński, R.; Duszyński, A.; Sakowska, J.; Zjawiony, J.K. Identification challenges in examination of commercial plant material of psychotria viridis. *Acta Pol. Pharm.,* **2015**, *72*(4), 747-755. [PMID: 26647632]

[29] Blainey, M.G. Forbidden therapies: Santo Daime, ayahuasca, and the prohibition of entheogens in Western society. *J. Relig. Health,* **2015**, *54*(1), 287-302. [http://dx.doi.org/10.1007/s10943-014-9826-2] [PMID: 24477460]

[30] Tupper, K.W.; Labate, B.C. Plants, psychoactive substances and the international narcotics control board: the control of nature and the nature of control. *Human Rights and Drugs.,* **2012**, *2*, 17-28.

[31] Ott, J. Pharmahuasca: human pharmacology of oral DMT plus harmine. *J. Psychoactive Drugs,* **1999**, *31*(2), 171-177. [http://dx.doi.org/10.1080/02791072.1999.10471741] [PMID: 10438001]

[32] Groisman, A.; de Rios, M.D. Ayahuasca, the U.S. Supreme Court, and the UDV-U.S. government case: Culture, religion, and implications of a legal dispute. Psychedelic Medicine: New Evidence for Hallucinogenic Substances as Treatments; Winkelman, M.J.; Rob-

erts, T.B., Eds.; Praeger Publishers: Westport, CT, **2007**, pp. 251-269.

[33] Bullis, R.K. The "vine of the soul" *vs*. the Controlled Substances Act: implications of the hoasca case. *J. Psychoactive Drugs,* **2008**, *40*(2), 193-199. [http://dx.doi.org/10.1080/02791072.2008.10400630] [PMID: 18720669]

[34] Tupper, K.W. Yahuasca, entheogenic education & public policy. 2011, (Ph.D, Simon Fraser University, Vancouver, British Columbia, Canada).

[35] Thomas, G.; Lucas, P.; Capler, N.R.; Tupper, K.W.; Martin, G. Ayahuasca-assisted therapy for addiction: results from a preliminary observational study in Canada. *Curr. Drug Abuse Rev.,* **2013**, *6*(1), 30-42. [http://dx.doi.org/10.2174/15733998113099990003] [PMID: 23627784]

[36] Anderson, B.T.; Labate, B.C.; Meyer, M.; Tupper, K.W.; Barbosa, P.C.; Grob, C.S.; Dawson, A.; McKenna, D. Statement on ayahuasca. *Int. J. Drug Policy,* **2012**, *23*(3), 173-175. [http://dx.doi.org/10.1016/j.drugpo.2012.02.007] [PMID: 22459485]

[37] Strassman, R. Subjective effects of DMT and the development of the hallucinogen rating scale *Newsletter Multidisciplinary Assoc. for Psychedelic Studies,* **1992**, *3*(2).

[38] Bresnick, T.; Levin, R. Phenomenal qualities of ayahuasca ingestion and its relation to fringe consciousness and personality. *Consciousness Studies,* **2006**, *13*(9), 5-24.

[39] Shanon, B. Altered temporality. *Consciousness Studies,* **2001**, *8*(1), 35-58.

[40] Riba, J.; Rodríguez-Fornells, A.; Urbano, G.; Morte, A.; Antonijoan, R.; Montero, M.; Callaway, J.C.; Barbanoj, M.J. Subjective effects and tolerability of the South American psychoactive beverage Ayahuasca in healthy volunteers. *Psychopharmacology (Berl.),* **2001**, *154*(1), 85-95. [http://dx.doi.org/10.1007/s002130000606] [PMID: 11292011]

[41] Beyer, S.V. Singing to the plants: A guide to Mestizo shamanism in the upper Amazon; University of New Mexico Press: Albuquerque, **2009**.

[42] Dos Santos, R.G.; Valle, M.; Bouso, J.C.; Nomdedéu, J.F.; Rodríguez-Espinosa, J.; McIlhenny, E.H.; Barker, S.A.; Barbanoj, M.J.; Riba, J. Autonomic, neuroendocrine, and immunological effects of ayahuasca: a comparative study with d-amphetamine. *J. Clin. Psychopharmacol.,* **2011**, *31*(6), 717-726. [http://dx.doi.org/10.1097/JCP.0b013e31823607f6] [PMID: 22005052]

[43] Dos Santos, R.G.; Grasa, E.; Valle, M.; Ballester, M.R.; Bouso, J.C.; Nomdedéu, J.F.; Homs, R.; Barbanoj, M.J.; Riba, J. Pharmacology of ayahuasca administered in two repeated doses. *Psychopharmacology (Berl.),* **2012**, *219*(4), 1039-1053. [http://dx.doi.org/10.1007/s00213-011-2434-x] [PMID: 21842159]

[44] Riba, J.; Rodríguez-Fornells, A.; Barbanoj, M.J. Effects of ayahuasca on sensory and sensorimotor gating in humans as measured by P50 suppression and prepulse inhibition of the startle reflex, respectively. *Psychopharmacology (Berl.),* **2002**, *165*(1), 18-28. [http://dx.doi.org/10.1007/s00213-002-1237-5] [PMID: 12474114]

[45] Metzner, R. Hallucinogenic drugs and plants in psychotherapy and shamanism. *J. Psychoactive Drugs,* **1998**, *30*(4), 333-341. [http://dx.doi.org/10.1080/02791072.1998.10399709] [PMID: 9924839]

[46] Strassman, R.J.; Qualls, C.R. Dose-response study of N,N-dimethyltryptamine in humans. I. Neuroendocrine, autonomic, and cardiovascular effects. *Arch. Gen. Psychiatry,* **1994**, *51*(2), 85-97. [http://dx.doi.org/10.1001/archpsyc.1994.03950020009001] [PMID: 8297216]

[47] 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. Pharmacokinetics of Hoasca alkaloids in healthy humans. *J. Ethnopharmacol.,* **1999**, *65*(3), 243-256. [http://dx.doi.org/10.1016/S0378-8741(98)00168-8] [PMID: 10404423]

[48] Rhodium Archive. 2009. A Hypothesis of the Mechanisms Underlying Visual Distortions Caused by Psychedelic Drugs. Available at http://www.erowid.org/archive/rhodium/pharmacology/ visual distortions.html

[49] Shanon, B. The antipodes of the mind: charting the phenomenology of the ayahuasca experience; Oxford University Press: Oxford, UK, **2007**.

[50] Cloninger, C.R. A systematic method for clinical description and classification of personality variants. A proposal. *Arch. Gen. Psychiatry,* **1987**, *44*(6), 573-588. [http://dx.doi.org/10.1001/archpsyc.1987.01800180093014] [PMID: 3579504]

[51] 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. Assessment of addiction severity among ritual users of ayahuasca. *Drug Alcohol Depend.,* **2010**, *111*(3), 257-261. [http://dx.doi.org/10.1016/j.drugalcdep.2010.03.024] [PMID: 20554400]

[52] Harris, R.; Gurel, L. A study of ayahuasca use in North America. *J. Psychoactive Drugs,* **2012**, *44*(3), 209-215. [http://dx.doi.org/10.1080/02791072.2012.703100] [PMID: 23061320]

[53] Barbosa, P.C.R.; Strassman, R.J.; da Silveira, D.X.; Areco, K.; Hoy, R.; Pommy, J.; Thoma, R.; Bogenschutz, M. Psychological and neuropsychological assessment of regular hoasca users. *Compr. Psychiatry,* **2016**, *71*, 95-105. [http://dx.doi.org/10.1016/j.comppsych.2016.09.003] [PMID: 27653781]

[54] Frecska, E.; Móré, C.E.; Vargha, A.; Luna, L.E. Enhancement of creative expression and entoptic phenomena as after-effects of repeated ayahuasca ceremonies. *J. Psychoactive Drugs,* **2012**, *44*(3), 191-199. [http://dx.doi.org/10.1080/02791072.2012.703099] [PMID: 23061318]

[55] Soler, J.; Elices, M.; Franquesa, A.; Barker, S.; Friedlander, P.; Feilding, A.; Pascual, J.C.; Riba, J. Exploring the therapeutic potential of Ayahuasca: acute intake increases mindfulness-related capacities. *Psychopharmacology (Berl.),* **2016**, *233*(5), 823-829. [http://dx.doi.org/10.1007/s00213-015-4162-0] [PMID: 26612618]

[56] Bouso, J.C.; González, D.; Fondevila, S.; Cutchet, M.; Fernández, X.; Ribeiro Barbosa, P.C.; Alcázar-Córcoles, M.Á.; Araújo, W.S.; Barbanoj, M.J.; Fábregas, J.M.; Riba, J. Personality, psychopathology, life attitudes and neuropsychological performance among ritual users of Ayahuasca: a longitudinal study. *PLoS One,* **2012**, *7*(8), e42421-e13. [http://dx.doi.org/10.1371/journal.pone.0042421] [PMID: 22905130]

[57] Kuypers, K.P.C.; Riba, J.; de la Fuente Revenga, M.; Barker, S.; Theunissen, E.L.; Ramaekers, J.G. Ayahuasca enhances creative divergent thinking while decreasing conventional convergent thinking. *Psychopharmacology (Berl.),* **2016**, *233*(18), 3395-3403. [http://dx.doi.org/10.1007/s00213-016-4377-8] [PMID: 27435062]

[58] Burton, J.C. Psychological variables predicting intensity and contents of consciousness during ayahuasca experiences: A pilot study. Dissertation Abstracts Int: Section B: Sci and Engineering, **2010**, *70*(9-B), 5882

[59] Loizaga-Velder, A.; Verres, R. Therapeutic effects of ritual ayahuasca use in the treatment of substance dependence--qualitative results. *J. Psychoactive Drugs,* **2014**, *46*(1), 63-72. [http://dx.doi.org/10.1080/02791072.2013.873157] [PMID: 24830187]

[60] Cavnar, C. The effects of participation in ayahuasca rituals on gay and lesbian identity. *J. Psychoactive Drugs,* **2014**, *46*, 252-260. [http://dx.doi.org/10.1080/02791072.2014.920117] [PMID: 25052884]

[61] Riba, J.; Anderer, P.; Morte, A.; Urbano, G.; Jané, F.; Saletu, B.; Barbanoj, M.J. Topographic pharmaco-EEG mapping of the effects of the South American psychoactive beverage ayahuasca in healthy volunteers. *Br. J. Clin. Pharmacol.,* **2002**, *53*(6), 613-628. [http://dx.doi.org/10.1046/j.1365-2125.2002.01609.x] [PMID: 12047486]

[62] dos Santos, R.G. Safety and side effects of ayahuasca in humans--an overview focusing on developmental toxicology. *J. Psychoactive Drugs,* **2013**, *45*(1), 68-78. [http://dx.doi.org/10.1080/02791072.2013.763564] [PMID: 23662333]

[63] Riba, J.; Anderer, P.; Jané, F.; Saletu, B.; Barbanoj, M.J. Effects of the South American psychoactive beverage ayahuasca on regional brain electrical activity in humans: a functional neuroimaging study using low-resolution electromagnetic tomography. *Neuropsychobiology,* **2004**, *50*(1), 89-101. [http://dx.doi.org/10.1159/000077946] [PMID: 15179026]

[64] Schenberg, E.E.; Alexandre, J.F.M.; Filev, R.; Cravo, A.M.; Sato, J.R.; Muthukumaraswamy, S.D.; Yonamine, M.; Waguespack, M.; Lomnicka, I.; Barker, S.A.; da Silveira, D.X. Acute blphasic effects of ayahuasca. *PLoS One,* **2015**, *10*(9), e0137202. [http://dx.doi.org/10.1371/journal.pone.0137202] [PMID: 26421727]

[65] Don, N.S.; McDonough, B.E.; Moura, G.; Warren, C.A.; Kawanishi, K.; Tomita, H.; Tachibana, Y.; Böhlke, M.; Farnsworth, N.R. Effects of Ayahuasca on the human EEG. *Phytomedicine,*

1998, *5*(2), 87-96. [http://dx.doi.org/10.1016/S0944-7113(98)80003-2] [PMID: 23195759]

[66] Stuckey, D.E. EEG gamma coherence and other correlates of subjective reports during ayahuasca experiences. Dissertation Abstracts Int: Section B: *Sci and Engineering*, **2005**, 66(1-B), 610.

[67] Valle, M.; Maqueda, A.E.; Rabella, M.; Rodríguez-Pujadas, A.; Antonijoan, R.M.; Romero, S.; Alonso, J.F.; Mañanas, M.À.; Barker, S.; Friedlander, P.; Feilding, A.; Riba, J. Inhibition of alpha oscillations through serotonin-2A receptor activation underlies the visual effects of ayahuasca in humans. *Eur. Neuropsychopharmacol.,* **2016**, *26*(7), 1161-1175. [http://dx.doi.org/10.1016/j.euroneuro.2016.03.012] [PMID: 27039035]

[68] Alonso, J.F.; Romero, S.; Mañanas, M.A.; Riba, J. Serotonergic psychedelics temporarily modify information transfer in humans. *Int. J. Neuropsychopharmacol.,* **2015**, *18*(8), pyv039. [http://dx.doi.org/10.1093/ijnp/pyv039] [PMID: 25820842]

[69] Riba, J.; Romero, S.; Grasa, E.; Mena, E.; Carrió, I.; Barbanoj, M.J. Increased frontal and paralimbic activation following ayahuasca, the pan-Amazonian inebriant. *Psychopharmacology (Berl.),* **2006**, *186*(1), 93-98. [http://dx.doi.org/10.1007/s00213-006-0358-7] [PMID: 16575552]

[70] Sanches, R.F.; de Lima Osório, F.; Dos Santos, R.G.; Macedo, L.R.; Maia-de-Oliveira, J.P.; Wichert-Ana, L.; de Araujo, D.B.; Riba, J.; Crippa, J.A.; Hallak, J.E. Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a SPECT study. *J. Clin. Psychopharmacol.,* **2016**, *36*(1), 77-81. [http://dx.doi.org/10.1097/JCP.0000000000000436] [PMID: 26650973]

[71] de Araujo, D.B.; Ribeiro, S.; Cecchi, G.A.; Carvalho, F.M.; Sanchez, T.A.; Pinto, J.P.; de Martinis, B.S.; Crippa, J.A.; Hallak, J.E.; Santos, A.C. Seeing with the eyes shut: neural basis of enhanced imagery following Ayahuasca ingestion. *Hum. Brain Mapp.,* **2012**, *33*(11), 2550-2560. [http://dx.doi.org/10.1002/hbm.21381] [PMID: 21922603]

[72] Bouso, J.C.; Palhano-Fontes, F.; Rodríguez-Fornells, A.; Ribeiro, S.; Sanches, R.; Crippa, J.A.; Hallak, J.E.; de Araujo, D.B.; Riba, J. Long-term use of psychedelic drugs is associated with differences in brain structure and personality in humans. *Eur. Neuropsychopharmacol.,* **2015**, *25*(4), 483-492. [http://dx.doi.org/10.1016/j.euroneuro.2015.01.008] [PMID: 25637267]

[73] Palhano-Fontes, F.; Andrade, K.C.; Tofoli, L.F.; Santos, A.C.; Crippa, J.A.; Hallak, J.E.; Ribeiro, S.; de Araujo, D.B. The psychedelic state induced by ayahuasca modulates the activity and connectivity of the default mode network. *PLoS One,* **2015**, *10*(2), e0118143. [http://dx.doi.org/10.1371/journal.pone.0118143] [PMID: 25693169]

[74] de Castro-Neto, E.F.; da Cunha, R.H.; da Silveira, D.X.; Yonamine, M.; Gouveia, T.L.; Cavalheiro, E.A.; Amado, D.; Naffah-Mazzacoratti, Mda.G. Changes in aminoacidergic and monoaminergic neurotransmission in the hippocampus and amygdala of rats after ayahuasca ingestion. *World J. Biol. Chem.,* **2013**, *4*(4), 141-147. [http://dx.doi.org/10.4331/wjbc.v4.i4.141] [PMID: 24340137]

[75] Domínguez-Clavé, E.; Soler, J.; Elices, M.; Pascual, J.C.; Álvarez, E.; de la Fuente Revenga, M.; Friedlander, P.; Feilding, A.; Riba, J. Ayahuasca: Pharmacology, neuroscience and therapeutic potential. *Brain Res. Bull.,* **2016**, *126*(Pt 1), 89-101. [http://dx.doi.org/10.1016/j.brainresbull.2016.03.002] [PMID: 26976063]

[76] Barbanoj, M.J.; Riba, J.; Clos, S.; Giménez, S.; Grasa, E.; Romero, S. Daytime Ayahuasca administration modulates REM and slow-wave sleep in healthy volunteers. *Psychopharmacology (Berl.),* **2008**, *196*(2), 315-326. [http://dx.doi.org/10.1007/s00213-007-0963-0] [PMID: 18030450]

[77] Luke, D. Discarnate entities and N,N-dimethyltryptamine (DMT): Psychopharmacology, phenomenology and ontology *Soc. Psychical. Res.,* **2011**, *75*(902[1]; 1), 26-42.

[78] Davis, M.; Bear, H.D. Effects of N-N-dimethyltryptamine on retention of startle response habituation in the rat. *Psychopharmacology (Berl.),* **1972**, *27*(1), 29-44. [http://dx.doi.org/10.1007/BF00421954] [PMID: 5081369]

[79] Davis, M.; Sheard, M.H. Biphasic dose-response effects of N-N-dimethyltryptamine on the rat startle reflex. *Pharmacol. Biochem. Behav.,* **1974**, *2*(6), 827-829. [http://dx.doi.org/10.1016/0091-3057(74)90116-6] [PMID: 4533618]

[80] Freedland, C.S.; Mansbach, R.S. Behavioral profile of constituents in ayahuasca, an Amazonian psychoactive plant mixture. *Drug Alcohol Depend.,* **1999**, *54*(3), 183-194. [http://dx.doi.org/10.1016/S0376-8716(98)00154-9] [PMID: 10372792]

[81] Morgenstern, J.; Langenbucher, J.; Labouvie, E.W. The generalizability of the dependence syndrome across substances: an examination of some properties of the proposed DSM-IV dependence criteria. *Addiction,* **1994**, *89*(9), 1105-1113. [http://dx.doi.org/10.1111/j.1360-0443.1994.tb02787.x] [PMID: 7987187]

[82] Fantegrossi, W.E.; Woods, J.H.; Winger, G. Transient reinforcing effects of phenylisopropylamine and indolealkylamine hallucinogens in rhesus monkeys. *Behav. Pharmacol.,* **2004**, *15*(2), 149-157. [http://dx.doi.org/10.1097/00008877-200403000-00007] [PMID: 15096915]

[83] Cole, J.M.; Pieper, W.A. the effects of N,N-dimenthyltryptamine on operant behaviour in squirrel monkeys. *Psychopharmacology (Berl.),* **1973**, *16*, 107-112. [http://dx.doi.org/10.1007/BF00422642]

[84] Gillin, J.C.; Cannon, E.; Magyar, R.; Schwartz, M.; Wyatt, R.J. Failure of N,N-dimethyltryptamine to evoke tolerance in cats. *Biol. Psychiatry,* **1973**, *7*(3), 213-220. [PMID: 4519415]

[85] Kovacic, B.; Domino, E.F. Tolerance and limited cross-tolerance to the effects of N, N-dimethyltryptamine (DMT) and lysergic acid diethylamide-25 (LSD) on food-rewarded bar pressing in the rat. *J. Pharmacol. Exp. Ther.,* **1976**, *197*(3), 495-502. [PMID: 1064726]

[86] Callaway, J.C.; Airaksinen, M.M.; McKenna, D.J.; Brito, G.S.; Grob, C.S. Platelet serotonin uptake sites increased in drinkers of ayahuasca. *Psychopharmacology (Berl.),* **1994**, *116*(3), 385-387. [http://dx.doi.org/10.1007/BF02245347] [PMID: 7892432]

[87] Strassman, R.J.; Qualls, C.R. Dose-response study of N,N-dimethyltryptamine in humans. I. Neuroendocrine, autonomic, and cardiovascular effects. *Arch. Gen. Psychiatry,* **1994**, *51*(2), 85-97. [http://dx.doi.org/10.1001/archpsyc.1994.03950020009001] [PMID: 8297216]

[88] Airaksinen, M.M.; Lecklin, A.; Saano, V.; Tuomisto, L.; Gynther, J. Tremorigenic effect and inhibition of tryptamine and serotonin receptor binding by beta-carbolines. *Pharmacol. Toxicol.,* **1987**, *60*(1), 5-8. [http://dx.doi.org/10.1111/j.1600-0773.1987.tb01711.x] [PMID: 3562389]

[89] Louis, E.D.; Zheng, W.; Jurewicz, E.C.; Watner, D.; Chen, J.; Factor-Litvak, P.; Parides, M. Elevation of blood beta-carboline alkaloids in essential tremor. *Neurology,* **2002**, *59*(12), 1940-1944. [http://dx.doi.org/10.1212/01.WNL.0000038385.60538.19] [PMID: 12499487]

[90] Bouso, J.C.; Fábregas, J.M.; Antonijoan, R.M.; Rodríguez-Fornells, A.; Riba, J. Acute effects of ayahuasca on neuropsychological performance: differences in executive function between experienced and occasional users. *Psychopharmacology (Berl.),* **2013**, *230*(3), 415-424. [http://dx.doi.org/10.1007/s00213-013-3167-9] [PMID: 23793226]

[91] Checkley, S.A.; Murray, R.M.; Oon, M.C.; Rodnight, R.; Birley, J.L. A longitudinal study of urinary excretion of N,N,-dimethyltryptamine in psychotic patients. *Br. J. Psychiatry,* **1980**, *137*, 236-239. [http://dx.doi.org/10.1192/bjp.137.3.236] [PMID: 6777009]

[92] Gillin, J.C.; Kaplan, J.; Stillman, R.; Wyatt, R.J. The psychedelic model of schizophrenia: the case of N,N-dimethyltryptamine. *Am. J. Psychiatry,* **1976**, *133*(2), 203-208. [http://dx.doi.org/10.1176/ajp.133.2.203] [PMID: 1062171]

[93] Paterson, N.E.; Darby, W.C.; Sandhu, P.S.N. N-Dimethyltryptamine-induced psychosis. *Clin. Neuropharmacol.,* **2015**, *38*(4), 141-143. [http://dx.doi.org/10.1097/WNF.0000000000000078] [PMID: 26166234]

[94] Warren, J.M.; Dham-Nayyar, P.; Alexander, J. Recreational use of naturally occurring dimethyltryptamine--contributing to psychosis? *Aust. N. Z. J. Psychiatry,* **2013**, *47*(4), 398-399. [http://dx.doi.org/10.1177/0004867412462749] [PMID: 23047957]

[95] Szmulewicz, A.G.; Valerio, M.P.; Smith, J.M. Switch to mania after ayahuasca consumption in a man with bipolar disorder: a case report. *Int. J. Bipolar Disord.,* **2015**, *3*, 4. [http://dx.doi.org/10.1186/s40345-014-0020-y] [PMID: 25713771]

[96] Flory, J.D.; Manuck, S.B.; Perel, J.M.; Muldoon, M.F. A comparison of d, l-fenfluramine and citalopram challenges in healthy

adults. *Psychopharmacology (Berl.),* **2004**, *174*(3), 376-380. [http://dx.doi.org/10.1007/s00213-003-1763-9] [PMID: 14997271]

[97] Mas, M.; Farré, M.; de la Torre, R.; Roset, P.N.; Ortuño, J.; Segura, J.; Camí, J. Cardiovascular and neuroendocrine effects and pharmacokinetics of 3, 4-methylenedioxymethamphetamine in humans. *J. Pharmacol. Exp. Ther.,* **1999**, *290*(1), 136-145. [PMID: 10381769]

[98] Davydova, S.M.; Cheido, M.A.; Gevorgyan, M.M. Effects of 5-HT2A receptor stimulation and blocking on immune response. *Bull Exp. Biol. Med.,* **2010**, *150*, 219-221.

[99] dos Santos, R.G. Immunological effects of ayahuasca in humans. *J. Psychoactive Drugs,* **2014**, *46*(5), 383-388. [http://dx.doi.org/10.1080/02791072.2014.960113] [PMID: 25364989]

[100] Frecska, E.; Szabo, A.; Winkelman, M.J.; Luna, L.E.; McKenna, D.J. A possibly sigma-1 receptor mediated role of dimethyltryptamine in tissue protection, regeneration, and immunity. *J. Neural Transm. (Vienna),* **2013**, *120*(9), 1295-1303. [http://dx.doi.org/10.1007/s00702-013-1024-y] [PMID: 23619992]

[101] Szabo, A.; Kovacs, A.; Frecska, E.; Rajnavolgyi, E. Psychedelic N,N-dimethyltryptamine and 5-methoxy-N,N-dimethyltryptamine modulate innate and adaptive inflammatory responses through the sigma-1 receptor of human monocyte-derived dendritic cells. *PLoS One,* **2014**, *9*(8), e106533. [http://dx.doi.org/10.1371/journal.pone.0106533] [PMID: 25171370]

[102] Szabo, A. Psychedelics and immunomodulation: novel approaches and therapeutic opportunities. *Front. Immunol.,* **2015**, *6*, 358. [http://dx.doi.org/10.3389/fimmu.2015.00358] [PMID: 26236313]

[103] House, R.V.; Thomas, P.T.; Bhargava, H.N. Comparison of the hallucinogenic indole alkaloids ibogaine and harmaline for potential immunomodulatory activity. *Pharmacology,* **1995**, *51*(1), 56-65. [http://dx.doi.org/10.1159/000139317] [PMID: 7568345]

[104] Rosenberg, D.E.; Isbell, H.; Miner, E.J. Comparison of a placebo, N,N-dimethyltryptamine, and 6-hydroxy-N-dimethyltryptamine in man. *Psychopharmacology (Berl.),* **1963**, *4*, 39-42. [http://dx.doi.org/10.1007/BF00429362] [PMID: 14050410]

[105] Rosenberg, D.E.; Isbell, H.; Miner, E.J.; Logan, C.R. The effect of N,N-dimethyltryptamine in human subjects tolerant to lysergic acid diethylamide. *Psychopharmacology (Berl.),* **1964**, *5*, 217-227. [http://dx.doi.org/10.1007/BF00413244] [PMID: 14138757]

[106] Bitsios, P.; Szabadi, E.; Bradshaw, C.M. Comparison of the effects of venlafaxine, paroxetine and desipramine on the pupillary light reflex in man. *Psychopharmacology (Berl.),* **1999**, *143*(3), 286-292. [http://dx.doi.org/10.1007/s002130050949] [PMID: 10353432]

[107] Hartley, T.R.; Lovallo, W.R.; Whitsett, T.L. Cardiovascular effects of caffeine in men and women. *Am. J. Cardiol.,* **2004**, *93*(8), 1022-1026. [http://dx.doi.org/10.1016/j.amjcard.2003.12.057] [PMID: 15081447]

[108] Pitol, D.L.; Siéssere, S.; Dos Santos, R.G.; Rosa, M.L.; Hallak, J.E.; Scalize, P.H.; Pereira, B.F.; Iyomasa, M.M.; Semprini, M.; Riba, J.; Regalo, S.C. Ayahuasca alters structural parameters of the rat aorta. *J. Cardiovasc. Pharmacol.,* **2015**, *66*(1), 58-62. [http://dx.doi.org/10.1097/FJC.0000000000000243] [PMID: 25714595]

[109] Mahmoudian, M.; Jalilpour, H.; Salehian, P. Toxicity of Peganum harmala: Review and a case report. *Iranian J. Pharmacol. Ther.,* **2002**, *1*, 1-4.

[110] Glennon, R.A.; Dukat, M.; Grella, B.; Hong, S.; Costantino, L.; Teitler, M.; Smith, C.; Egan, C.; Davis, K.; Mattson, M.V. Binding of beta-carbolines and related agents at serotonin (5-HT(2) and 5-HT(1A)), dopamine (D(2)) and benzodiazepine receptors. *Drug Alcohol Depend.,* **2000**, *60*(2), 121-132. [http://dx.doi.org/10.1016/S0376-8716(99)00148-9] [PMID: 10940539]

[111] Chen, X.; Cromer, B.A.; Lynch, J.W. Molecular determinants of β-carboline inhibition of the glycine receptor. *J. Neurochem.,* **2009**, *110*(5), 1685-1694. [http://dx.doi.org/10.1111/j.1471-4159.2009.06273.x] [PMID: 19619142]

[112] Pic-Taylor, A.; da Motta, L.G.; de Morais, J.A.; Junior, W.M.; Santos, Ade.F.; Campos, L.A.; Mortari, M.R.; von Zuben, M.V.; Caldas, E.D. Behavioural and neurotoxic effects of ayahuasca infusion (*Banisteriopsis caapi* and *Psychotria viridis*) in female Wistar rat. *Behav. Processes,* **2015**, *118*, 102-110. [http://dx.doi.org/10.1016/j.beproc.2015.05.004] [PMID: 26049017]

[113] Sklerov, J.; Levine, B.; Moore, K.A.; King, T.; Fowler, D. A fatal intoxication following the ingestion of 5-methoxy-N,N-dimethyltryptamine in an ayahuasca preparation. *J. Anal. Toxicol.,* **2005**, *29*(8), 838-841. [http://dx.doi.org/10.1093/jat/29.8.838] [PMID: 16356341]

[114] Warren, R.J. Fatal nicotine intoxication resulting from the ingestion of "ayahuasca". *J. Anal. Toxicol.,* **2004**, *28*, 287.

[115] Dos Santos, R.G. Toxicity of chronic ayahuasca administration to the pregnant rat: how relevant it is regarding the human, ritual use of ayahuasca? *Birth Defects Res. B Dev. Reprod. Toxicol.,* **2010**, *89*(6), 533-535. [http://dx.doi.org/10.1002/bdrb.20272] [PMID: 21136499]

[116] Oliveira, C.D.; Moreira, C.Q.; de Sá, L.R.; Spinosa, Hde.S.; Yonamine, M. Maternal and developmental toxicity of ayahuasca in Wistar rats. *Birth Defects Res. B. Dev. Reprod. Toxicol.,* **2010**, *89*(3), 207-212. [http://dx.doi.org/10.1002/bdrb.20244] [PMID: 20549682]

[117] Gardner, D.; Riet-Correa, F.; Lemos, D.; Welch, K.; Pfister, J.; Panter, K. Teratogenic effects of Mimosa tenuiflora in a rat model and possible role of N-methyl- and N,N-dimethyltryptamine. *J. Agric. Food Chem.,* **2014**, *62*(30), 7398-7401. [http://dx.doi.org/10.1021/jf5005176] [PMID: 24689494]

[118] Riba, J.; McIlhenny, E.H.; Valle, M.; Bouso, J.C.; Barker, S.A. Metabolism and disposition of N,N-dimethyltryptamine and harmala alkaloids after oral administration of ayahuasca. *Drug Test. Anal.,* **2012**, *4*(7-8), 610-616. [http://dx.doi.org/10.1002/dta.1344] [PMID: 22514127]

[119] Herraiz, T.; González, D.; Ancín-Azpilicueta, C.; Arán, V.J.; Guillén, H. beta-Carboline alkaloids in Peganum harmala and inhibition of human monoamine oxidase (MAO). *Food Chem. Toxicol.,* **2010**, *48*(3), 839-845. [http://dx.doi.org/10.1016/j.fct.2009.12.019] [PMID: 20036304]

[120] Gaujac, A.; Navickiene, S.; Collins, M.I.; Brandt, S.D.; de Andrade, J.B. Analytical techniques for the determination of tryptamines and β-carbolines in plant matrices and in psychoactive beverages consumed during religious ceremonies and neo-shamanic urban practices. *Drug Test. Anal.,* **2012**, *4*(7-8), 636-648. [http://dx.doi.org/10.1002/dta.1343] [PMID: 22577086]

[121] Callaway, J.C. Various alkaloid profiles in decoctions of Banisteriopsis caapi. *J. Psychoactive Drugs,* **2005**, *37*(2), 151-155. [http://dx.doi.org/10.1080/02791072.2005.10399796] [PMID: 16149328]

[122] McIlhenny, E.H.; Pipkin, K.E.; Standish, L.J.; Wechkin, H.A.; Strassman, R.; Barker, S.A. Direct analysis of psychoactive tryptamine and harmala alkaloids in the Amazonian botanical medicine ayahuasca by liquid chromatography-electrospray ionization-tandem mass spectrometry. *J. Chromatogr. A,* **2009**, *1216*(51), 8960-8968. [http://dx.doi.org/10.1016/j.chroma.2009.10.088] [PMID: 19926090]

[123] McKenna, D.J.; Towers, G.H.; Abbott, F. Monoamine oxidase inhibitors in South American hallucinogenic plants: tryptamine and beta-carboline constituents of ayahuasca. *J. Ethnopharmacol.,* **1984**, *10*(2), 195-223. [http://dx.doi.org/10.1016/0378-8741(84)90003-5] [PMID: 6587171]

[124] Wang, Y.H.; Samoylenko, V.; Tekwani, B.L.; Khan, I.A.; Miller, L.S.; Chaurasiya, N.D.; Rahman, M.M.; Tripathi, L.M.; Khan, S.I.; Joshi, V.C.; Wigger, F.T.; Muhammad, I. Composition, standardization and chemical profiling of Banisteriopsis caapi, a plant for the treatment of neurodegenerative disorders relevant to Parkinson's disease. *J. Ethnopharmacol.,* **2010**, *128*(3), 662-671. [http://dx.doi.org/10.1016/j.jep.2010.02.013] [PMID: 20219660]

[125] Misra, P.; Khaliq, T.; Dixit, A.; SenGupta, S.; Samant, M.; Kumari, S.; Kumar, A.; Kushawaha, P.K.; Majumder, H.K.; Saxena, A.K.; Narender, T.; Dube, A. Antileishmanial activity mediated by apoptosis and structure-based target study of peganine hydrochloride dihydrate: an approach for rational drug design. *J. Antimicrob. Chemother.,* **2008**, *62*(5), 998-1002. [http://dx.doi.org/10.1093/jac/dkn319] [PMID: 18694906]

[126] Carbonaro, T.M.; Gatch, M.B. Neuropharmacology of N,N-dimethyltryptamine. *Brain Res. Bull.,* **2016**, *126*(Pt 1), 74-88. [http://dx.doi.org/10.1016/j.brainresbull.2016.04.016] [PMID: 27126737]

[127] Saavedra, J.M.; Axelrod, J. Psychotomimetic N-methylated tryptamines: formation in brain *in vivo* and *in vitro*. *Science,* **1972**, *175*(4028), 1365-1366. [http://dx.doi.org/10.1126/science.175.4028.1365] [PMID: 5059565]

[128] Fontanilla, D.; Johannessen, M.; Hajipour, A.R.; Cozzi, N.V.; Jackson, M.B.; Ruoho, A.E. The hallucinogen N,N-dimethyltryptamine (DMT) is an endogenous sigma-1 receptor regulator. *Science,* **2009**, *323*(5916), 934-937. [http://dx.doi.org/10.1126/science.1166127] [PMID: 19213917]

[129] Keiser, M.J.; Setola, V.; Irwin, J.J.; Laggner, C.; Abbas, A.I.; Hufeisen, S.J.; Jensen, N.H.; Kuijer, M.B.; Matos, R.C.; Tran, T.B.; Whaley, R.; Glennon, R.A.; Hert, J.; Thomas, K.L.; Edwards, D.D.; Shoichet, B.K.; Roth, B.L. Predicting new molecular targets for known drugs. *Nature,* **2009**, *462*(7270), 175-181. [http://dx.doi.org/10.1038/nature08506] [PMID: 19881490]

[130] Carbonaro, T.M.; Eshleman, A.J.; Forster, M.J.; Cheng, K.; Rice, K.C.; Gatch, M.B. The role of 5-HT2A, 5-HT 2C and mGlu2 receptors in the behavioral effects of tryptamine hallucinogens N,N-dimethyltryptamine and N,N-diisopropyltryptamine in rats and mice. *Psychopharmacology (Berl.),* **2015**, *232*(1), 275-284. [http://dx.doi.org/10.1007/s00213-014-3658-3] [PMID: 24985890]

[131] Strassman, R.J.; Qualls, C.R.; Berg, L.M. Differential tolerance to biological and subjective effects of four closely spaced doses of N,N-dimethyltryptamine in humans. *Biol. Psychiatry,* **1996**, *39*(9), 784-795. [http://dx.doi.org/10.1016/0006-3223(95)00200-6] [PMID: 8731519]

[132] Bunzow, J.R.; Sonders, M.S.; Arttamangkul, S.; Harrison, L.M.; Zhang, G.; Quigley, D.I.; Darland, T.; Suchland, K.L.; Pasumamula, S.; Kennedy, J.L.; Olson, S.B.; Magenis, R.E.; Amara, S.G.; Grandy, D.K. Amphetamine, 3,4-methylenedioxymethamphetamine, lysergic acid diethylamide, and metabolites of the catecholamine neurotransmitters are agonists of a rat trace amine receptor. *Mol. Pharmacol.,* **2001**, *60*(6), 1181-1188. [http://dx.doi.org/10.1124/mol.60.6.1181] [PMID: 11723224]

[133] Premont, R.T.; Gainetdinov, R.R.; Caron, M.G. Following the trace of elusive amines. *Proc. Natl. Acad. Sci. USA,* **2001**, *98*(17), 9474-9475. [http://dx.doi.org/10.1073/pnas.181356198] [PMID: 11504935]

[134] Schenberg, E.E. Ayahuasca and cancer treatment. *SAGE Open Med.,* **2013**, *1*, 2050312113508389. [http://dx.doi.org/10.1177/2050312113508389] [PMID: 26770688]

[135] Tittarelli, R.; Mannocchi, G.; Pantano, F.; Romolo, F.S. Recreational use, analysis and toxicity of tryptamines. *Curr. Neuropharmacol.,* **2015**, *13*(1), 26-46. [http://dx.doi.org/10.2174/1570159X13666141210222409] [PMID: 26074742]

[136] Langer, S.Z.; Lee, C.R.; Segonzac, A.; Tateishi, T.; Esnaud, H.; Schoemaker, H.; Winblad, B. Possible endocrine role of the pineal gland for 6-methoxytetrahydro-beta-carboline, a putative endogenous neuromodulator of the [3H]imipramine recognition site. *Eur. J. Pharmacol.,* **1984**, *102*(2), 379-380. [http://dx.doi.org/10.1016/0014-2999(84)90275-9] [PMID: 6090167]

[137] Frison, G.; Favretto, D.; Zancanaro, F.; Fazzin, G.; Ferrara, S.D. A case of beta-carboline alkaloid intoxication following ingestion of Peganum harmala seed extract. *Forensic Sci. Int.,* **2008**, *179*(2-3), e37-e43. [http://dx.doi.org/10.1016/j.forsciint.2008.05.003] [PMID: 18603389]

[138] Anderson, B.T. Ayahuasca as antidepressant? Psychedelics and styles of reasoning in psychiatry. *Anthropol. Consciousness,* **2012**, *23*(1), 44-59. [http://dx.doi.org/10.1111/j.1556-3537.2012.01056.x]

[139] Rodd, R. Reassessing the cultural and psychopharmacological significance of Banisteriopsis caapi: preparation, classification and use among the Piaroa of Southern Venezuela. *J. Psychoactive Drugs,* **2008**, *40*(3), 301-307. [http://dx.doi.org/10.1080/02791072.2008.10400645] [PMID: 19004422]

[140] Brierley, D.I.; Davidson, C. Developments in harmine pharmacology--implications for ayahuasca use and drug-dependence treatment. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2012**, *39*(2), 263-272. [http://dx.doi.org/10.1016/j.pnpbp.2012.06.001] [PMID: 22691716]

[141] Drucker, G.; Raikoff, K.; Neafsey, E.J.; Collins, M.A. Dopamine uptake inhibitory capacities of beta-carboline and 3,4-dihydro-beta-carboline analogs of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) oxidation products. *Brain Res.,* **1990**, *509*(1), 125-133. [http://dx.doi.org/10.1016/0006-8993(90)90318-6] [PMID: 2137718]

[142] Bain, J.; Plater, L.; Elliott, M.; Shpiro, N.; Hastie, C.J.; McLauchlan, H.; Klevernic, I.; Arthur, J.S.; Alessi, D.R.; Cohen, P. The selectivity of protein kinase inhibitors: a further update. *Biochem. J.,* **2007**, *408*(3), 297-315. [http://dx.doi.org/10.1042/BJ20070797] [PMID: 17850214]

[143] Husbands, S.M.; Glennon, R.A.; Gorgerat, S.; Gough, R.; Tyacke, R.; Crosby, J.; Nutt, D.J.; Lewis, J.W.; Hudson, A.L. beta-carboline binding to imidazoline receptors. *Drug Alcohol Depend.,* **2001**, *64*(2), 203-208. [http://dx.doi.org/10.1016/S0376-8716(01)00123-5] [PMID: 11543990]

[144] Hopp, K.H.; Cunningham, L.V.; Bromel, M.C.; Schermeister, L.J.; Khalil, S.K. *In vitro* antitrypanosomal activity of certain alkaloids against Trypanosoma lewisi. *Lloydia,* **1976**, *39*(5), 375-377. [PMID: 798093]

[145] Li, Y.; Sattler, R.; Yang, E.J.; Nunes, A.; Ayukawa, Y.; Akhtar, S.; Ji, G.; Zhang, P.W.; Rothstein, J.D. Harmine, a natural beta-carboline alkaloid, upregulates astroglial glutamate transporter expression. *Neuropharmacology,* **2011**, *60*(7-8), 1168-1175. [http://dx.doi.org/10.1016/j.neuropharm.2010.10.016] [PMID: 21034752]

[146] Schwarz, M.J.; Houghton, P.J.; Rose, S.; Jenner, P.; Lees, A.D. Activities of extract and constituents of *Banisteriopsis caapi* relevant to parkinsonism. *Pharmacol. Biochem. Behav.,* **2003**, *75*(3), 627-633. [http://dx.doi.org/10.1016/S0091-3057(03)00129-1] [PMID: 12895680]

[147] Brierley, D.I.; Davidson, C. Harmine augments electrically evoked dopamine efflux in the nucleus accumbens shell. *J. Psychopharmacol. (Oxford),* **2013**, *27*(1), 98-108. [http://dx.doi.org/10.1177/0269881112463125] [PMID: 23076833]

[148] Grella, B.; Dukat, M.; Young, R.; Teitler, M.; Herrick-Davis, K.; Gauthier, C.B.; Glennon, R.A. Investigation of hallucinogenic and related beta-carbolines. *Drug Alcohol Depend.,* **1998**, *50*(2), 99-107. [http://dx.doi.org/10.1016/S0376-8716(97)00163-4] [PMID: 9649961]

[149] Iurlo, M.; Leone, G.; Schilström, B.; Linnér, L.; Nomikos, G.; Hertel, P.; Silvestrini, B.; Svensson, H. Effects of harmine on dopamine output and metabolism in rat striatum: role of monoamine oxidase-A inhibition. *Psychopharmacology (Berl.),* **2001**, *159*(1), 98-104. [http://dx.doi.org/10.1007/s002130100879] [PMID: 11797076]

[150] Schmitt, K.C.; Reith, M.E. Regulation of the dopamine transporter: aspects relevant to psychostimulant drugs of abuse. *Ann. N. Y. Acad. Sci.,* **2010**, *1187*, 316-340. [http://dx.doi.org/10.1111/j.1749-6632.2009.05148.x] [PMID: 20201860]

[151] Adayev, T.; Wegiel, J.; Hwang, Y.W. Harmine is an ATP-competitive inhibitor for dual-specificity tyrosine phosphorylation-regulated kinase 1A (Dyrk1A). *Arch. Biochem. Biophys.,* **2011**, *507*(2), 212-218. [http://dx.doi.org/10.1016/j.abb.2010.12.024] [PMID: 21185805]

[152] Göckler, N.; Jofre, G.; Papadopoulos, C.; Soppa, U.; Tejedor, F.J.; Becker, W. Harmine specifically inhibits protein kinase DYRK1A and interferes with neurite formation. *FEBS J.,* **2009**, *276*(21), 6324-6337. [http://dx.doi.org/10.1111/j.1742-4658.2009.07346.x] [PMID: 19796173]

[153] Frost, D.; Meechoovet, B.; Wang, T.; Gately, S.; Giorgetti, M.; Shcherbakova, I.; Dunckley, T. β-carboline compounds, including harmine, inhibit DYRK1A and tau phosphorylation at multiple Alzheimer's disease-related sites. *PLoS One,* **2011**, *6*(5), e19264. [http://dx.doi.org/10.1371/journal.pone.0019264] [PMID: 21573099]

[154] Réus, G.Z.; Stringari, R.B.; de Souza, B.; Petronilho, F.; Dal-Pizzol, F.; Hallak, J.E.; Zuardi, A.W.; Crippa, J.A.; Quevedo, J. Harmine and imipramine promote antioxidant activities in prefrontal cortex and hippocampus. *Oxid. Med. Cell. Longev.,* **2010**, *3*(5), 325-331. [http://dx.doi.org/10.4161/oxim.3.5.13109] [PMID: 21150338]

[155] Callaway, J.C. Fast and slow metabolizers of Hoasca. *J. Psychoactive Drugs,* **2005**, *37*(2), 157-161. [http://dx.doi.org/10.1080/02791072.2005.10399797] [PMID: 16149329]

[156] Yu, A.M.; Idle, J.R.; Krausz, K.W.; Küpfer, A.; Gonzalez, F.J. Contribution of individual cytochrome P450 isozymes to the O-demethylation of the psychotropic beta-carboline alkaloids harmaline and harmine. *J. Pharmacol. Exp. Ther.,* **2003**, *305*(1), 315-322. [http://dx.doi.org/10.1124/jpet.102.047050] [PMID: 12649384]

[157] Zhao, T.; Zheng, S.S.; Zhang, B.F.; Li, Y.Y.; Bligh, S.W.; Wang, C.H.; Wang, Z.T. Metabolic pathways of the psychotropic-carboline alkaloids, harmaline and harmine, by liquid chromatography/mass spectrometry and NMR spectroscopy. *Food Chem.,*

2012, *134*(2), 1096-1105. [http://dx.doi.org/10.1016/j.foodchem.2012.03.024] [PMID: 23107733]

[158] Winstock, A.R.; Kaar, S.; Borschmann, R. Dimethyltryptamine (DMT): prevalence, user characteristics and abuse liability in a large global sample. *J. Psychopharmacol. (Oxford),* **2014**, *28*(1), 49-54. [http://dx.doi.org/10.1177/0269881113513852] [PMID: 24284475]

[159] Gable, R.S. Comparison of acute lethal toxicity of commonly abused psychoactive substances. *Addiction,* **2004**, *99*(6), 686-696. [http://dx.doi.org/10.1111/j.1360-0443.2004.00744.x] [PMID: 15139867]

[160] Lanaro, R.; Calemi, D.B.; Togni, L.R.; Costa, J.L.; Yonamine, M.; Cazenave, Sde.O.; Linardi, A. Ritualistic use of ayahuasca versus street use of similar substances seized by the police: a key factor involved in the potential for intoxications and overdose? *J. Psychoactive Drugs,* **2015**, *47*(2), 132-139. [http://dx.doi.org/10.1080/02791072.2015.1013202] [PMID: 25950593]

[161] Erspamer, V. Observations on the fate of indolalkylamines in the organism. *J. Physiol.,* **1955**, *127*(1), 118-133. [http://dx.doi.org/10.1113/jphysiol.1955.sp005242] [PMID: 14354632]

[162] Riba, J.; McIlhenny, E.H.; Bouso, J.C.; Barker, S.A. Metabolism and urinary disposition of N,N-dimethyltryptamine after oral and smoked administration: a comparative study. *Drug Test. Anal.,* **2015**, *7*(5), 401-406. [http://dx.doi.org/10.1002/dta.1685] [PMID: 25069786]

[163] Callaway, J.C.; Grob, C.S. Ayahuasca preparations and serotonin reuptake inhibitors: a potential combination for severe adverse interactions. *J. Psychoactive Drugs,* **1998**, *30*(4), 367-369. [http://dx.doi.org/10.1080/02791072.1998.10399712] [PMID: 9924842]

[164] Zhao, T.; He, Y.Q.; Wang, J.; Ding, K.M.; Wang, C.H.; Wang, Z.T. Inhibition of human cytochrome P450 enzymes 3A4 and 2D6 by β-carboline alkaloids, harmine derivatives. *Phytother. Res.,* **2011**, *25*(11), 1671-1677. [http://dx.doi.org/10.1002/ptr.3458] [PMID: 21433154]

[165] Liester, M.B.; Prickett, J.I. Hypotheses regarding the mechanisms of ayahuasca in the treatment of addictions. *J. Psychoactive Drugs,* **2012**, *44*(3), 200-208. [http://dx.doi.org/10.1080/02791072.2012.704590] [PMID: 23061319]

[166] Stahl, S.M. Stahl's essential psychopharmacology: Neuroscientific basic and practical applications; Cambridge University Press: Cambridge, UK, **2008**.

[167] Glick, S.D.; Kuehne, M.E.; Raucci, J. Effects of iboga alkaloids on morphine and cocaine self-administration in rats: relationship to tremorigenic effects and to effects on dopamine release in nucleus accumbens and striatum, *Brain Res.,* **1994**, *657*, 14-22.

[168] Halpern, J.H. Hallucinogens in the treatment of alcoholism and other addictions. Psychedelic Medicine: New Evidence for Hallucinogenic Substances as Treatments; Winkelman, M.J.; Roberts, T.B., Eds.; Praeger: Westport, CT, **2007**, Vol. 2.

[169] Doering-Silveira, E.; Grob, C.S.; de Rios, M.D.; Lopez, E.; Alonso, L.K.; Tacla, C.; Da Silveira, D.X. Report on psychoactive drug use among adolescents using ayahuasca within a religious context. *J. Psychoactive Drugs,* **2005**, *37*(2), 141-144. [http://dx.doi.org/10.1080/02791072.2005.10399794] [PMID: 16149326]

[170] Oliveira-Lima, A.J.; Santos, R.; Hollais, A.W. Effects of ayahuasca on the development of ethanol-induced behavioral sensitization and on a post-sensitization treatment in mice. *Physiol. Behav.,* **2015**, *142*, 28-36.

[171] Aricioglu-Kartal, F.; Kayir, H.; Tayfun Uzbay, I. Effects of harman and harmine on naloxone-precipitated withdrawal syndrome in morphine-dependent rats. *Life Sci.,* **2003**, *73*(18), 2363-2371. [http://dx.doi.org/10.1016/S0024-3205(03)00647-7] [PMID: 12941438]

[172] Miralles, A.; Esteban, S.; Sastre-Coll, A.; Moranta, D.; Asensio, V.J.; García-Sevilla, J.A. High-affinity binding of beta-carbolines to imidazoline I2B receptors and MAO-A in rat tissues: norharman blocks the effect of morphine withdrawal on DOPA/noradrenaline synthesis in the brain. *Eur. J. Pharmacol.,* **2005**, *518*(2-3), 234-242. [http://dx.doi.org/10.1016/j.ejphar.2005.06.023] [PMID: 16061219]

[173] Osório, Fde.L.; Sanches, R.F.; Macedo, L.R.; Santos, R.G.; Maia-de-Oliveira, J.P.; Wichert-Ana, L.; Araujo, D.B.; Riba, J.; Crippa, J.A.; Hallak, J.E. Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report. *Br. J. Psychiatry,* **2015**, *37*(1), 13-20. [http://dx.doi.org/10.1590/1516-4446-2014-1496] [PMID: 25806551]

[174] Dos Santos, R.G.; Osório, F.L.; Crippa, J.A.S.; Riba, J.; Zuardi, A.W.; Hallak, J.E.C. Antidepressive, anxiolytic, and antiaddictive effects of ayahuasca, psilocybin and lysergic acid diethylamide (LSD): a systematic review of clinical trials published in the last 25 years. *Ther. Adv. Psychopharmacol.,* **2016**, *6*(3), 193-213. [http://dx.doi.org/10.1177/2045125316638008] [PMID: 27354908]

[175] Santos, R.G.; Landeira-Fernandez, J.; Strassman, R.J.; Motta, V.; Cruz, A.P. Effects of ayahuasca on psychometric measures of anxiety, panic-like and hopelessness in Santo Daime members. *J. Ethnopharmacol.,* **2007**, *112*(3), 507-513. [http://dx.doi.org/10.1016/j.jep.2007.04.012] [PMID: 17532158]

[176] Farzin, D.; Mansouri, N. Antidepressant-like effect of harmane and other beta-carbolines in the mouse forced swim test. *Eur. Neuropsychopharmacol.,* **2006**, *16*(5), 324-328. [http://dx.doi.org/10.1016/j.euroneuro.2005.08.005] [PMID: 16183262]

[177] Fortunato, J.J.; Réus, G.Z.; Kirsch, T.R.; Stringari, R.B.; Stertz, L.; Kapczinski, F.; Pinto, J.P.; Hallak, J.E.; Zuardi, A.W.; Crippa, J.A.; Quevedo, J. Acute harmine administration induces antidepressive-like effects and increases BDNF levels in the rat hippocampus. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2009**, *33*(8), 1425-1430. [http://dx.doi.org/10.1016/j.pnpbp.2009.07.021] [PMID: 19632287]

[178] Fortunato, J.J.; Réus, G.Z.; Kirsch, T.R.; Stringari, R.B.; Fries, G.R.; Kapczinski, F.; Hallak, J.E.; Zuardi, A.W.; Crippa, J.A.; Quevedo, J. Chronic administration of harmine elicits antidepressant-like effects and increases BDNF levels in rat hippocampus. *J. Neural Transm. (Vienna),* **2010**, *117*(10), 1131-1137. [http://dx.doi.org/10.1007/s00702-010-0451-2] [PMID: 20686906]

[179] Fortunato, J.J.; Réus, G.Z.; Kirsch, T.R.; Stringari, R.B.; Fries, G.R.; Kapczinski, F.; Hallak, J.E.; Zuardi, A.W.; Crippa, J.A.; Quevedo, J. Effects of beta-carboline harmine on behavioral and physiological parameters observed in the chronic mild stress model: further evidence of antidepressant properties. *Brain Res. Bull.,* **2010**, *81*(4-5), 491-496. [http://dx.doi.org/10.1016/j.brainresbull.2009.09.008] [PMID: 19772900]

[180] Osório, F.L.; de Macedo, L.R.H.; de Sousa, J.P.M.; Pinto, J. Quevedo. J.; Crippa, J.A.d.S.; Hallak, J.C.E. The therapeutic potential of harmine and ayahuasca in depression: Evidence from exploratory animal and human studies. The ethnopharmacology of ayahuasca; dos Santos, R.G., Ed.; Transworld Research Network: Kerala, India, **2011**, pp. 75-85.

[181] Samoylenko, V.; Rahman, M.M.; Tekwani, B.L.; Tripathi, L.M.; Wang, Y.H.; Khan, S.I.; Khan, I.A.; Miller, L.S.; Joshi, V.C.; Muhammad, I. *Banisteriopsis caapi*, a unique combination of MAO inhibitory and antioxidative constituents for the activities relevant to neurodegenerative disorders and Parkinson's disease. *J. Ethnopharmacol.,* **2010**, *127*(2), 357-367. [http://dx.doi.org/10.1016/j.jep.2009.10.030] [PMID: 19879939]

[182] Urani, A.; Roman, F.J.; Phan, V.L.; Su, T.P.; Maurice, T. The antidepressant-like effect induced by sigma(1)-receptor agonists and neuroactive steroids in mice submitted to the forced swimming test. *J. Pharmacol. Exp. Ther.,* **2001**, *298*(3), 1269-1279. [PMID: 11504830]

[183] Wang, J.; Mack, A.L.; Coop, A.; Matsumoto, R.R. Novel sigma (sigma) receptor agonists produce antidepressant-like effects in mice. *Eur. Neuropsychopharmacol.,* **2007**, *17*(11), 708-716. [http://dx.doi.org/10.1016/j.euroneuro.2007.02.007] [PMID: 17376658]

[184] Piletz, J.E.; Zhu, H.; Ordway, G.; Stockmeier, C.; Dilly, G.; Reis, D.; Halaris, A. Imidazoline receptor proteins are decreased in the hippocampus of individuals with major depression. *Biol. Psychiatry,* **2000**, *48*(9), 910-919. [http://dx.doi.org/10.1016/S0006-3223(00)00892-1] [PMID: 11074229]

[185] Finn, D.P.; Martí, O.; Harbuz, M.S.; Vallès, A.; Belda, X.; Márquez, C.; Jessop, D.S.; Lalies, M.D.; Armario, A.; Nutt, D.J.; Hudson, A.L. Behavioral, neuroendocrine and neurochemical effects of the imidazoline I2 receptor selective ligand BU224 in naive rats and rats exposed to the stress of the forced swim test. *Psychopharmacology (Berl.),* **2003**, *167*(2), 195-202. [http://dx.doi.org/10.1007/s00213-003-1392-3] [PMID: 12652345]

[186] Halaris, A.; Piletz, J.E. Relevance of imidazoline receptors and agmatine to psychiatry: A decade of progress. *A. N. Y. Acad. Sci.,* **2003**, *1009*, 1-20.

[187] Paterson, L.M.; Robinson, E.S.; Nutt, D.J.; Hudson, A.L. *In vivo* estimation of imidazoline(2) binding site turnover. *Ann. N. Y. Acad. Sci.,* **2003**, *1009*, 367-370. [http://dx.doi.org/10.1196/annals.1304.049] [PMID: 15028614]

[188] García-Sevilla, J.A.; Escribá, P.V.; Guimón, J. Imidazoline receptors and human brain disorders. *Ann. N. Y. Acad. Sci.,* **1999**, *881*, 392-409. [http://dx.doi.org/10.1111/j.1749-6632.1999.tb09388.x] [PMID: 10415944]

[189] Bouayed, J.; Rammal, H.; Soulimani, R. Oxidative stress and anxiety: relationship and cellular pathways. *Oxid. Med. Cell. Longev.,* **2009**, *2*(2), 63-67. [http://dx.doi.org/10.4161/oxim.2.2.7944] [PMID: 20357926]

[190] Jacob, M.S.; Presti, D.E. Endogenous psychoactive tryptamines reconsidered: An anxiolytic role for dimethyltryptamine *Med Hypothesis,* **2005**, *64*(5), 930-937. *Hypothesis,* **2005**, *64*(5), 930-937. [http://dx.doi.org/10.1016/j.mehy.2004.11.005]

[191] Sarris, J.; McIntyre, E.; Camfield, D.A. Plant-based medicines for anxiety disorders, part 2: a review of clinical studies with supporting preclinical evidence. *CNS Drugs,* **2013**, *27*(4), 301-319. [http://dx.doi.org/10.1007/s40263-013-0059-9] [PMID: 23653088]

[192] Santos, R.G.; Landeira-Fernandez, J.; Strassman, R.J.; Motta, V.; Cruz, A.P. Effects of ayahuasca on psychometric measures of anxiety, panic-like and hopelessness in Santo Daime members. *J. Ethnopharmacol.,* **2007**, *112*(3), 507-513. [http://dx.doi.org/10.1016/j.jep.2007.04.012] [PMID: 17532158]

[193] Graeff, F.G.; Guimarães, F.S.; De Andrade, T.G.; Deakin, J.F. Role of 5-HT in stress, anxiety, and depression. *Pharmacol. Biochem. Behav.,* **1996**, *54*(1), 129-141. [http://dx.doi.org/10.1016/0091-3057(95)02135-3] [PMID: 8728550]

[194] Metzner, R. Hallucinogenic drugs and plants in psychotherapy and shamanism. *J. Psychoactive Drugs,* **1998**, *30*(4), 333-341. [http://dx.doi.org/10.1080/02791072.1998.10399709] [PMID: 9924839]

[195] Nutt, D.J.; King, L.A.; Nichols, D.E. Effects of Schedule I drug laws on neuroscience research and treatment innovation. *Nat. Rev. Neurosci.,* **2013**, *14*(8), 577-585. [http://dx.doi.org/10.1038/nrn3530] [PMID: 23756634]

[196] Dos Santos, R.G.; Balthazar, F.M.; Bouso, J.C.; Hallak, J.E.C. The current state of research on ayahuasca: A systematic review of human studies assessing psychiatric symptoms, neuropsychological functioning, and neuroimaging. *J. Psychopharmacol. (Oxford),* **2016**, *30*(12), 1230-1247. [http://dx.doi.org/10.1177/0269881116652578] [PMID: 27287824]

[197] Heise, C.W.; Brooks, D.E. Ayahuasca exposure: Descriptive analysis of calls to US poison control centers from 2005 to 2015. *J. Med. Toxicol*., **2017**, *13*, 245-248.