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Review On Pharmacological Potential of a Traditional Amazonian Decoction: Ayahuasca

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ABSTRACT:

Background: The psychedelic beverage known as Ayahuasca is also referred to as a "master plant." It originates out of the Amazon Basin. Ayahuasca is the Quechua term that refers to "vine of soul". It is a hallucinogenic decoction prepared by a combination of stems and bark of *Banisteriopsis caapi*, containing beta-carboline alkaloids and leaves of *Psychotria viridis*, supplying the hallucinogen N, N-dimethyltryptamine (DMT).
Shamans perform rituals using Ayahuasca as a herbal beverage. Participants in the sessions have a favourable opinion of its application. Ayahuasca's therapeutic effects primarily depend on the mechanisms of tryptamines' potent serotonergic actions. The monoamine-oxidase A (MAO-A) inhibitory characteristics of beta-carbolines and DMT work together to produce psychedelic effects.
The majority of recent scientific study that supports the potential advantages attributed to it has been conducted in the domains of clinical psychology, neurology, and psychopharmacology. With expanding use and interest in Ayahuasca, it's critical to comprehend its safety, psychological effects, and possible clinical applications.
Objective: As it has spiritual connectivity and the belief of shamans this review provides a scientific perspective by studying Ayahuasca's pharmacological potential, therapeutic uses, possible adverse effects, proposed mechanisms of action, and potential clinical uses in mental illness.
Conclusion: Ayahuasca has pharmacological effects on various body systems leading to subjective effects and curing other psychological disorders. It may prove to be an effective quintessential component in the fields of ethnopharmacology, biomedicine, and psychiatry. It has an impact on human evolution.

Keywords: Ayahuasca, DMT, shamans, pharmacological potential, decoction, MAO-inhibitors, *Banisteriopsis caapi, Psychotria viridis,* hallucinogens.

I. INTRODUCTION:

Traditional herbal medicine has been used by societies all over the world for millennia to meet their healthcare needs. Despite modern scientific and technical developments, the market for herbal medicines and supplements has grown worldwide, particularly in Amazonian countries. The Quechua phrase "Ayahuasca" means "vine of soul," "vine of spirits," or "vine of dead"[1]. It is used by indigenous tribes in north-western Amazonian nations including Brazil, Peru, Colombia, and Ecuador for healing in the framework of ethnomedical practises as well as for rites of passage, divination, battle, and magical-religious practises[2].

A decoction with psychoactive characteristics that affects all the senses, alters one's thinking, consciousness of time, emotional ritual, religious, and therapeutic objectives, and causes one to hallucinate was first created by indigenous people of the Amazon basin. The medication also has severe autonomic effects that include mydriasis, an increase in blood pressure, heart rate, and rectal temperature[3]. According to studies, healing rituals are enabling people to reach a degree of spirituality that would usually require years of focused study and meditation. Additionally, it gives them a new outlook on life that cannot be obtained with conventional medications or a contemporary lifestyle.

This concoction is used beyond the native spheres of the Amazon. Populations' acceptance of globalisation has encouraged cultural interaction between Western practises and indigenous traditions, which has resulted in the ritual, religious, and therapeutic usage of Ayahuasca. As the interest in people attending Ayahuasca rituals has increased, the number of indigenous healers known as curanderos or shamans and Western facilitators provide Ayahuasca sessions to a wider and more diversified audience.

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II. CHEMICAL CONSTITUENTS AND MECHANISM ASSOCIATED WITH THE BIOLOGICAL ACTION OF AYAHUASCA:

Banisteriopsis caapi stems and bark, which contain beta-carboline alkaloids harmala, harmine, harmaline, and tetrahydro harmine, as well as *Psychotria viridis* leaves, which supply the hallucinogen N, N-dimethyltryptamine, or DMT, are combined and boiled and reduced for several hours to create the brew[4]. Ayahuasca has dozens of indigenous names, also known by the terms of hoasca or oasca, caapi or kahpi, natema or natem, daime etc[5].

Native Amazonian populations have had a genuine understanding of the combined activity of the two plant species for at least 3000 years[6]. Tetra hydro harmine functions as a mild serotonin reuptake inhibitor without having any MAOI effect, whereas the harmala alkaloids harmine and harmaline are monoamine oxidase inhibitors (MAOIs), without which the DMT would be inactivated by the gut and liver monoamine oxidase (MAOs).

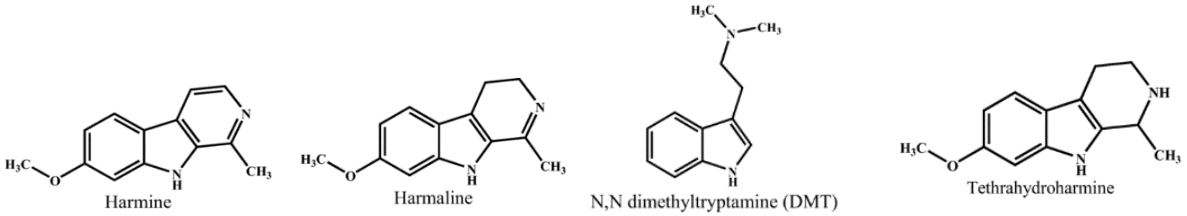

Figure 1: Chemical structures of the Ayahuasca components[7].

Tryptamines and carboline molecules, which are consumed simultaneously, are the main active ingredients in Ayahuasca, thus understanding how they interact is crucial. When taken orally, DMT is typically eliminated by the liver MAO; however, when combined with -carbolines, this inhibitory impact of the liver MAO over DMT is avoided. Generally speaking, beta-carbolines function as reversible inhibitors of the A-type isoenzyme of the MAO in addition to the SSRI (selective serotonin reuptake inhibitor) action. According to studies, the therapeutic effects of Ayahuasca are mostly based on processes of tryptamines' potent serotonergic actions, acting on both serotonin (5-HT) receptors and trace amine-associated receptors (TAAR6)[8].

DMT has anxiolytic effects while MAO inhibition has depressive effects via a 5-HT1A receptor agonism. Agonists for 5-HT1A and 5-HT2A receptors include substances like 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT). When used with MAO inhibitors, 5-MeO-DMT causes a delay in hyperactivity and a reduction in locomotor activity. Ayahuasca decoction may have antiparkinsonian effects in addition to having various therapeutic benefits for other neurodegenerative diseases, according to certain theories. The central nervous system's increased tryptamine concentration, altered pharmacokinetic action brought on by MAO inhibitors, and increased interaction with other target areas can all be attributed to Ayahuasca's hallucinogenic effects[9].

Sigma receptors (Sig-1R), collaborative molecules found in the brain, retina, heart, liver, and immune system, mediate several signalling pathways, including neuronal development, stress response, oxidative stress, and apoptosis. They may also have a role in the action of DMT and other tryptamines[10].

III. TAXONOMICAL CLASSIFICATION AND PREPARATION OF DECOCTION

In the majority of syncretic churches, Ayahuasca is typically prepared from the bark of *Banisteriopsis caapi* (Malpighiaceae) and *Psychotria Viridis* (Rubiaceae). First, pieces (bark) of B. caapi are gathered, cleaned in water, and then carefully added to leaves of P. viridis that have also been cleaned. To create several litres of the brew, the plant material is then covered with water, which is then added to the mixture. The concoction is then cooked and concentrated for at least 8 hours. The end product is essentially a black extract. The majority of clinical and experimental research prepared Ayahuasca similarly, making a decoction for oral administration (120 to 125 mL/patient) during rituals in accordance with local customs[11].

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Table 1: Taxonomical classification of the plants

Sr.no	Taxonomic category	Plant-1	Plant-2
1.	Kingdom	Plantae	Plantae
2.	Class	Angiosperms	Angiosperms
3.	Order	Malpighiales	Gentianales
4.	Family	Malpighiaceae	Rubiaceae
5.	Genus	Banisteriopsis	Psychotria
6.	Species	Caapi	Viridis
7.	Binomial name	*Banisteriopsis caapi*[12]	*Psychotria viridis*[13]

IV. PHARMACOLOGICAL POTENTIAL OF THE BEVERAGE:

Researchers discovered four known beta-carbolines—harmine, harmaline, tetrahydroharmine, and harmol—as well as two new beta-carboline alkaloidal glycosides (Banisteride A and B) and related acetates. They also discovered a fifth beta-carboline—tetrahydro norharmine. 8.8 to 42 mg of DMT, 17 to 280 mg of harmine, 4.6 to 28 mg of harmaline, and 4.2 to 150 mg of tetrahydroharmine were found to be present in Ayahuasca. The many plant parts and various preparation techniques are responsible for these significant compositional variances. Chemical profiling of the aqueous extract from the stems of *Banisteriopsis caapi* revealed a variety of new compounds[14]. The toxic dose of Ayahuasca for a 75 kg person would be roughly 7.8 litres. However, since vomiting and diarrhoea start occurring long before this limit is reached and because they have a very unpleasant taste, no one can ever reach this level[15].

DMT is probably a natural sigma-1 receptor ligand that inhibits psychosis and promotes a calmer, more relaxed state of mind. Although this receptor is present in the brain, lung, prostate, colon, ovaries, breasts, and liver, it is not fully understood how it works. This receptor might be involved in cancer, anxiety, and depression. The receptor is located on the endoplasmic reticulum membrane associated with mitochondria, but when triggered by ligands in high concentrations, they may go to the cell's plasma membrane, where they inhibit a number of ion channels. DMT has also shown an affinity for α1- and α2-adrenergic receptors as well as the dopamine D1 receptor[16].

According to a recent study Ayahuasca decreased levels of glycine and GABA neurotransmitter levels in the hippocampus and amygdala of rats. It increases GABA levels in the hippocampus, which causes a decrease in GABA release, and it increases neurotransmitter release in the amygdala, which increases the inhibitory action. Due to the significance of these limbic structures in neuronal pathways involved in memory, learning, and emotion, these opposing effects on the degree of inhibitory neurotransmission in these two limbic structures provide an explanation for the behavioural effects of Ayahuasca[17].

Compared to Ayahuasca, which caused a cognitive peak between 60 and 120 minutes with effects lasting roughly four hours, DMT had a rapid beginning of action whether delivered intravenously or when smoked, with a peak cognitive effect lasting for about 3–10 minutes. Additionally, this beverage causes somatic side effects, such as nausea, tingling, and an increase in body temperature, which start to manifest around 20 minutes after ingestion[18]. It is clear from the information provided above that Ayahuasca may be the solution to a number of physical and psychological conditions.

V. PHARMACOLOGICAL EFFECTS OF AYAHUASCA ON THE HUMAN BODY

While the subjective effects of Ayahuasca start to be felt within 30 minutes of consumption, the effects of inhaled DMT are visible within seconds of

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inhalation. Ayahuasca sessions frequently extend for 4 to 6 hours, with the peak intensity of effects frequently perceived at roughly 1.5 hours after consumption. Subjective effects usually fade away within 20 minutes. Beyond the known pharmacological qualities of the plants, Amazonian traditions hold that the ritual or ceremonial components have an impact on the experience. Different parts of our body are affected differently by it[19].

1.Effect on Brain: The brew affects awareness, prompting recurrence of unpleasant memories and the emergence of fresh viewpoints on issues generating emotional discomfort. For effective visualisation and problem-solving strategies for a peaceful future, it causes changes in numerous brain areas that are involved in feelings, memory, vision, consciousness, and problem-solving related to past and present life events. The amygdala uses monoamines to evoke memories that are fully emotional. The neocortex portion of the brain, for example, exhibits greater activity as evidenced by changes in perception, cognition, behaviour, and reasoning[20].

According to some theories, Ayahuasca can have both direct and indirect effects on serotonergic and dopaminergic neurons in the mesolimbic pathway, which can have an anti-addictive impact[19]. Additionally, it has been discovered that Ayahuasca alters γ□aminobutyric acid (GABA) concentrations, with amygdala GABA release increasing and hippocampus GABA release decreasing, which has effects on learning, memory, and emotional functions[21]. Ayahuasca potentially activates prefrontal and temporal regions of the brain and increases blood flow in frontal and paralimbic regions, which may be mediated by glutamate release[22].

2.Effect on Endocrine System: Cortisol rises to a maximum at 60 minutes and falls to basal levels at 360 minutes. It boosts both GH (growth hormone) and prolactin, but returns to baseline by 360 minutes. GH and prolactin levels are influenced by the serotonergic system. The effects of DMT and other serotonergic medications are to blame for this surge[11].

3.Effect on Immune System: With large increases in natural killer (NK) cells, significant decreases in both CD3 and CD4 lymphocytes at 1.5 and 2 hours, and no significant changes in CD8 or CD19 lymphocytes, Ayahuasca raises total lymphocytes at 1.5 hours and decreases them at 4.5 hours. The ability of T helper 1 and T helper 17 cells to trigger immunological responses was compromised by DMT and 5-MeO-DMT[23]. It was observed that harmaline reduced CD8 activity, interleukin (IL-2 and IL-4) production, B cell proliferation, and NK cell activity in a dose-related manner[24].

Consuming Ayahuasca raises blood cortisol and prolactin levels, which have a variety of biological effects, including immune system modulation. Some types of depression have been linked to abnormally low cortisol levels, or hypocortisolaemia, and the up-regulation of cortisol expression that occurs after ingesting Ayahuasca may contribute to the substance's antidepressant effects[25]. Consuming Ayahuasca may result in higher amounts of lymphocyte and natural killer cell redistribution. Such observations point to a potential anti-inflammatory mechanism of action that may be helpful in treating PNEI (psych neuroendocrine immune) system disorders, including particular subtypes of depression[26].

4.Effect on Pupil Size and Body Temperature: Several Ayahuasca research has shown mydriasis. Pupil diameter increased up to 4.9 + 0.2 mm at 180 minutes and returned to normal by 360 minutes. Elevation of pupil size is dose-dependent. The mean PLR amplitude decreased, while the pupillary light reflex (PLR) latency was increased. These modifications are related to. Body temperature was statistically significantly lowered by DMT for the first hour, then gradually rose[27].

5.Effect on Cardiovascular System: Following consumption of Ayahuasca containing 0.85 mg/kg of DMT, diastolic blood pressure (DBP) rose to its highest level by about 10 mmHg at 15 minutes and its highest level by about 8 mmHg at 75 minutes. Oral consumption exhibited faster HR and BP elevations, which were determined to be dose-dependent[28].

VI. SUBJECTIVE AND PHYSIOLOGICAL EFFECTS OF AYAHUASCA / PHENOMENOLOGY:

Something subjective is based more on the individual's thoughts and feelings than on objective reality. Euphoria, relaxation, and having less inhibition are common positive subjective sensations. It refers to researching the positive changes a person experiences following an Ayahuasca ritual. There are several negative subjective feelings, such as nausea, breathing difficulties, light-headedness, and depression. It entails research on the grim changes that the person is experiencing.

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The physiological consequences show how the body responds to the beverage and investigate hormonal adjustments. The subjective effects of DMT are strongly influenced by surroundings, which is consistent with the behaviour of classic psychedelics. Accordingly, a negative environment and mindset prior to consumption are more likely to result in adverse subjective effects, and vice versa, a positive build-up and environment are typically more likely to result in a positive subjective experience[21]. A stimulant's typical initial effects can include increased heart rate and blood pressure, bewilderment, anxiety, and a feeling of being overpowered. Soon after taking DMT, the user may experience kinaesthetic hallucinations, such as sensations of vibration, auditory hallucinations, such as hearing music or vibrating sounds, and frequent visions of kaleidoscopic intertwined geometric patterns[29].

Phenomenology of DMT and Ayahuasca[30]:

- Complicated visuals,
- Interactions with conscious beings (the vast majority of living things susceptible to delusion, misery, and reincarnation),
- Disembodiment, out-of-body experience (OBE) is a sensation of your consciousness leaving your body
- Patterns of geometry,
- Change the perception of time and space
- Sensed indicators of presence
- Having a dreamy quality,
- Losing one's sense of self and becoming one with the universe
- Synaesthesia (the phenomenon of experiencing one sense via another).
- Sensitivity to emotion

Table 2: Positive, Negative and Physiological effects[31]

A. Positive subjective effects:	B. Negative subjective effects:	C. Physiological effects:
1. examination of one's own thoughts and feelings. 2. calm/peaceful 3. autobiographical memories; 4. feelings of well-being and happiness 5. Synaesthesia (a difference in how colors and sounds are perceived) 6. Mystical or religious encounter	1.Solicitude, terror agony. 2. lunatic	1. Lower amounts of CD3 and CD4 lymphocytes. 2. a little rise in BP and HR 3. A rise in the number of natural killer cells 4. A rise in the release of cortisol, prolactin, and GH 5. elevation of body temperature 6. dilation of the pupil

VII. THERAPEUTIC USES OF AYAHUASCA

In healthy people, Ayahuasca use has been proven to be connected with high levels of overall wellbeing. Obsessive-compulsive, neurotic, depressed, somatic, anxious, interpersonal sensitive, hopeless, hostile, phobic, paranoid, and psychotic symptoms are rated lower in Ayahuasca users, who also have reduced psychopathology[32]. Long-term Ayahuasca usage has been linked to improved neuropsychological test results, particularly in the areas of working memory and attention. Ayahuasca use has also been linked to improved creativity and a stronger capacity for overcoming sorrow, according to reports[22]. Ayahuasca is a hallucinogenic narcotic, but interestingly, studies have shown that it reduces reliance on users and can help treat addictions to other substances like alcohol and cocaine[33]. Ayahuasca may be helpful for people with mental issues such as stress-associated disorders, depression, and anxiety, according to a number of tiny modern investigations of people in related religions, indigenous ceremonial situations, and in therapeutic settings[34]. Additionally, psoriasis, dermatitis, and Crohn's illness have all been linked to the PNEI system, and case studies have shown that Ayahuasca is effective in treating these conditions[35].

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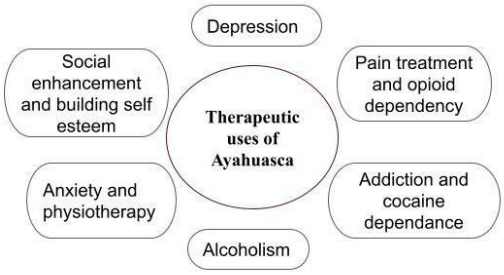

Figure 2: Therapeutic uses of Ayahuasca

VIII. ADVERSE EFFECT:

People who have a personal or family history of psychotic illness or who are currently experiencing any psychotic symptoms are typically not allowed to use Ayahuasca in the traditional contexts. The most frequent unpleasant effects of Ayahuasca are nausea and vomiting, which are frequently accompanied by additional somatic-dysphoric sensations including feeling hot or cold or having stomach pain. Vomiting is not seen negatively in ceremonial circumstances; rather, it is seen as a cleaning procedure[36]. Vomiting was noted in 4 out of 53 Ayahuasca administrations in early laboratory experiments utilising freeze-dried Ayahuasca (7.5%)[37]. Only nine of the enrolled volunteers completed the trial in a subsequent study by the same team that involved the administration of two doses of Ayahuasca spaced four hours apart, and five of them were excluded from the study due to vomiting[38]. The only side effect that was noted in our open-label trial, which involved giving a single dosage of Ayahuasca to 17 patients with treatment-resistant major depressive disorder, was vomiting, which happened in 47% of the volunteers[20]. In our second randomised controlled trial, nausea (71%), vomiting (57%), brief anxiety (50%), brief headache (42%), and restlessness (50%) were the most frequent adverse effects[39].

IX. CONCLUSION:

Due to the widespread use of Ayahuasca in the developing world, there are significant clinical questions regarding the drug's potential therapeutic and pharmacological applications. In the areas of ethnopharmacology, biomedicine, and psychiatry, Ayahuasca may prove to be a successful and optimal component. It may seem inappropriate to study hallucinogens, but as some researchers have suggested recently, investigating the unusual effects of psychoactive substances like Ayahuasca has the potential to be helpful in the treatment of many psychiatric and medical illnesses. Online polls and recent research indicate that Ayahuasca usage is linked to advantages across the gamut of psychological and mindfulness-based criteria, as well as improvements in overall well-being.

Its therapeutic potential for addiction and mental health disorders is being studied more and more. However, despite research confirming its low toxicity, there are some risks associated with Ayahuasca use. These include the dangers of combining analogue drugs to produce a more intense experience, inexperienced users ordering it online, a lack of support before and after the experience, misinformation about potential interactions (for example, particularly with serotonergic anti-depressants), and contraindications with certain medical and mental health conditions. This essay examines the potential advantages and risks of using Ayahuasca.

If Amazonian healing is to be incorporated into modern healthcare systems, safety and efficacy standards must be met, and some form of regulatory monitoring must be devised due to the potential of misuse and substandard therapeutic results.

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