

Ayahuasca – potential therapeutic properties in psychiatry. Research review

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Summary

Ayahuasca, also known as “the liana of the soul” and “the vine of the soul” is a ritual psychedelic traditionally administered in the form of plant decoction, used by the indigenous people of South America for centuries, and in the last 25 years also in Europe, Asia, Africa, Australia, Canada, and the United States. Its biological activity results from the content of N,N-dimethyltryptamine (DMT), acting mainly as a non-selective agonist of serotonin receptors and beta-carboline alkaloids, which are strong and short-acting monoamine oxidase type A (MAOI-A) inhibitors. For many years there have been reports of both the anti-anxiety and antidepressant effects of ayahuasca, as well as indications of the possibility of its use in the treatment of addictions. The results of studies of its effectiveness in drug-resistant depression seem to be promising, comparable in the opinion of some authors with the effect of therapeutic action of ketamine. In the article, we try to explain the complex profile of action and the resulting potential benefits, but also the risk of interaction and adverse effects associated with the taking of ayahuasca, which is important given the high variability of herbal mixtures used to produce the decoction.

Key words: ayahuasca, DMT

Introduction

Ayahuasca is a ritual psychedelic used by the people of South America for centuries. Traditionally, it is administered in the form of a decoction during a few hours of night rituals, which are led by a shaman providing spiritual support, what increases the therapeutic effect of meetings [1]. The two largest religious associations practicing rituals are Unia Do Vegetal (UDV) and Santo Daime, whose branches are spread all over the world. However, only in Brazil (since 1987) and the United

States (since 2006) it is legally permissible to use ayahuasca provided that it is used for religious purposes only. In Poland, the ingredients of the decoction are on the list of narcotic and psychoactive substances. Ayahuasca is characterized by poor tolerance from the digestive system causing vomiting, nausea and diarrhea. Traditionally this is considered to be its 'purification' effect [2]. It also causes an increase in blood pressure, heart rate [3], increases body temperature and the concentration of prolactin and cortisol [4].

This paper summarizes the literature collected on the basis of a review of the Medline/Pubmed database. PubMed database was searched using the following terms: 'ayahuasca', 'hoasca', 'DMT', 'N,N-dimethyltryptamine', 'psychedelics'. Materials appearing from 1987 to November 2018 were analyzed.

DMT and beta-carboline alkaloids: pharmacodynamics, pharmacokinetics

Most often a blend of plants *Banisteriopsis caapi* and *Psychotria viridis* or *Diplopterys cabrerana* is used for the preparation of ayahuasca brew. Psychoactive effects of *Psychotria viridis* and *Diplopterys cabrerana* is associated with the presence of DMT, a tryptamine derivative that is a non-selective agonist of serotonergic receptors, mainly 5-HT_{2A} [5]. The substance also has affinity for receptors σ 1 [6], α 1 and α 2-adrenergic, dopamine D1 [7] and trace amine receptors TAARs [8]. Although DMT is in a very small amount produced in the human body, there is insufficient information about the biosynthesis and biochemical properties of its endogenous form. In general, DMT in the human body is very rapidly metabolized and inactivated regardless of the way of administration. After injection, the duration of action is 15–60 minutes, after inhalation – up to 30 minutes [9]. When administered orally, it has no biological activity due to its rapid metabolism to inactive forms through the gastrointestinal and hepatic monoamine oxidase (MAO). In the composition of ayahuasca, there is also *Banisteriopsis caapi*, containing a group of beta-carboline alkaloids: harmaline, harmine and tetrahydroharmine. Alkaloids, as a potent and short-acting MAO-A inhibitors, slow down the metabolism of DMT and allow it to function after oral administration after 20 minutes, reaching a peak between 1 and 2 hours and ending after about 4–5 hours [4]. Beta-carboline alkaloids also have affinity for 5-HT_{2A/C} receptors, dopamine transporters and imidazole receptors I2 [2].

Side effects

Ayahuasca can cause serious, life-threatening side effects. By acting as MAOI it increases the risk of serotonin syndrome. Also it has been shown to interact with selective serotonin reuptake inhibitors [10]. The occurrence of symptoms of serotonin and myoclonic syndrome after administration of beta-carboline alkaloids with tryptophan has been described in rodents [11]. Harmine, as a substrate and inhibitor of CYP2D6 [12, 13], can cause interaction with its other substrates. Randomized

research in which ayahuasca was administered to people in the form of lyophilized extract showed its acceptable safety [2]. It was estimated that the lethal dose is about 20 times higher than the average dose administered during rituals [14]. So far, no death has been reported in ayahuasca clinical research. Several documented cases of death have been described, including suicide, after ritual use of ayahuasca, in which their causal relationship cannot be clearly identified [1]. They do not contain key information, such as the blood analysis for beta-carboline alkaloids, the composition of the decoction and the dose ingested, which limits the possibility of drawing final conclusions [15]. In other words, there are no documented data showing clearly ayahuasca poisoning as the cause of death. On the other hand, the analysis of 538 cases reported by telephone to the US Poison Control Centers from 2005 to 2015 related to ayahuasca is disturbing [16]. It shows that 63% of reports were related to moderate or severe somatic and psychopathological symptoms, in which 28 cases required intubation, 12 had seizure, 7 – respiratory arrest, 4 – cardiac arrest. Three fatalities were reported. It should be emphasized, however, that the report covers only telephone notification, without a detailed analysis. It is not known what mixture of plants or what substances exactly were used.

Psychomimetic effects

Gable [14], on the basis of a 5-year observation of UDV members, concluded that ayahuasca does not increase the risk of long-term psychosis. In the analyzed documentation, containing an exposure to 25,000 portions of decoction (without specifying the number of people, only exposure), from 13 to 24 cases were reported in which the substance could contribute to the induction of psychotic episodes. When comparing the result with the risk of schizophrenia in the general population, Gable postulates that consuming ayahuasca cannot be considered as a trigger for permanent psychosis. Lima et al. [17] came to a similar conclusion in a report analyzing cases of psychotic disorders among UDV members from 1994–2007. There is a report of paranoid syndrome after ritual consumption of ayahuasca preceded by a 6-year of cannabinoids intake period [18] and mania with psychotic symptoms preceded by a 10-day hypomanic episode in a person confirming their occurrence in the past [19]. Two psychosis cases with features of manic-paranoid syndrome after simultaneous intake of DMT and cannabinoids have also been published [20, 21]. So far, in clinical trials, there were no cases of correlation between ayahuasca or DMT and chronic psychosis, which can be explained by an accurate interview of clinical trial participants towards possible predisposing factors for psychosis [18].

Addiction – risk vs. therapeutic properties

So far, the physical addictive effect of ayahuasca has not been demonstrated, and no withdrawal symptoms have been observed in available studies [14, 22, 23].

It does not activate the reward system in the striatum and the ventral tegmental area, it only increases the flow of blood in the frontal and paralimbic areas, as shown in the single-photon emission computed tomography (SPECT) [24]. It is assumed, however, that ayahuasca can demonstrate addictive potential through positive reinforcement. 15–20% of people taking part in the ritual for the first time become members of UDV [14]. Rodent research provides encouraging data on the potential benefits of its use in addiction. There have been reports of a reduction in the symptoms of cocaine and morphine dependence when administering harmine in rats [25] as well as the inhibition of the development of alcohol addiction behavior in ayahuasca-treated mice [26, 27]. Available clinical reports based on surveys (which reduces the value of this information) prove that ayahuasca may show therapeutic effects in people addicted to other psychoactive substances [22, 28–31]. However, it is difficult to separate the action of the substance itself from the psychological effect of the symbolism of the ritual or the significance of the collective therapeutic factor [22, 32, 33].

Long-term effects of ayahuasca

Studies of people using ritual decoction show that the long-term effect is a reduction in the severity of psychopathological symptoms, mainly in terms of mood and anxiety [23, 28, 34]. The respondents also describe better psychosocial and pro-health functioning [23, 31, 35, 36]. Regular ayahuasca users achieve better results in cognitive function tests [37]. Riba et al. [38] published a randomized clinical trial based on the regional cerebral blood flow observed in SPECT, during which fifteen volunteers, previously using ayahuasca, were orally administered its capsule at a dose corresponding to 1.0 mg DMT/kg body weight or placebo. Significant activation of the frontal and paralimbic areas was found 100–110 minutes later. The results of neuroimaging examinations of 22 people who took ayahuasca at least 50 times in the last 2 years were compared to the results of 22 people who did not use this substance, there were no differences in their age, gender, education and level of intelligence. Significant differences in the thickness of the cortex in the brain, especially in structures forming the default mode network (DMN) have been demonstrated. They were correlated with the intensity and duration of ayahuasca use [39].

DMN is the area of the brain responsible for internally oriented mental processes whose increased activity is found in depression, schizophrenia, social phobia, and reduced activity – during meditation and hypnosis. Palhano-Fontes et al. [40] document the results of research showing a decrease in DMN activity in the functional magnetic resonance imaging after ayahuasca administration.

Antidepressant effect – experimental research

Experimental studies on animal models of depression have shown that chronic administration of harmine reduces anergy and anhedonia as well as increases adrenal

mass and BDNF levels in the rodent hippocampus [41, 42], which suggests antidepressant effect [34]. In vitro studies of progenitor cells of adult rodents have shown that the alkaloids of *Banisteriopsis caapi* stimulate neurogenesis. This effect is comparable to the effect of antidepressants [43]. Cameron L.P et al. [44] studied the influence of DMT on rat behavior, confirming its antidepressant and anxiolytic effect.

In 2017, research was published [45] on the validated animal model of depression in primates (*Callitrix jacchus*) with hypocortisolemia, which were given nortriptyline for 7 days and a single dose of ayahuasca. Ayahuasca has been shown to increase cortisol levels up to 48 hours after administration. It also shows a stronger antidepressant effect, faster and more lasting hypocortisolemia compared to nortriptyline. In a juvenile animal model of depression presented by de Silva et al. ayahuasca presented beneficial long-lasting antidepressant effect [46].

Antidepressant effect – research in humans

There are reports [43, 47] of a rapid, already occurring after the first exposure, antidepressant effect of ayahuasca in patients diagnosed with drug-resistant depression. The effect is noticeable after 1 hour of administration and lasts up to 21 days [24, 47]. In 2018 a randomized, double-blind trial among 29 patients with confirmed drug-resistant depression was published. Single doses of placebo or ayahuasca containing 0.36 mg/ml DMT, 1.86 mg/ml harmine, 0.24 mg/ml harmaline and 1.20 mg/ml tetrahydroharmine were administered, showing a rapid antidepressant effect, persisting up to day 7 after a single administration. According to the authors [34], the obtained results are comparable to the effect of therapeutic action of ketamine in drug-resistant depression.

In a study of 17 depressed [24] patients, 8 hours after a single administration of 2.2 ml/kg of ayahuasca, there was an increased SPECT blood flow in the brain areas responsible for mood and emotions, and there was a significant reduction in the severity of illness symptoms during the period of time from 80 minutes to 21 days after administration.

In vitro studies [48] of human progenitor nerve cells derived from human pluripotent stem cells showed that harmine after a 4-day experiment increased their proliferation by 71.5%.

The results of a randomized trial [49] have been also published. The authors of the study assumed that hypocortisolemia is specific for drug-resistant depression, and showed an increase in salivary cortisol level after the administration of a single dose of ayahuasca, in which the concentration of DMT was 0.36 mg/ml, harmine – 1.86 mg/ml, harmaline – 0.24 mg/ml, and tetrahydroharmine – 1.20 mg/ml.

Conclusions

As it has been shown, the ayahuasca components seem to have a potential therapeutic value in the treatment of mental illnesses and disorders. However, due to the

small number of research groups and randomized trials, this results should be approached with caution. An additional difficulty in continuing work on this issue are legal restrictions. The United Nations recommends having DMT only for scientific and medical purposes. In Poland, *Banisteriopsis caapi* and *Psychotria viridis* can be used only for medical and scientific purposes, but DMT only for the purpose of scientific research. This may result in the inability to carry out extensive clinical trials, as well as to prevent the use of these substances in pharmacotherapy, as is the case with cannabinoids.

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