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REVIEW ARTICLE

Antidepressive and anxiolytic effects of ayahuasca: a systematic literature review of animal and human studies

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Objective: To conduct a systematic literature review of animal and human studies reporting anxiolytic or antidepressive effects of ayahuasca or some of its isolated alkaloids (dimethyltryptamine, harmine, tetrahydroharmine, and harmaline).
Methods: Papers published until 3 April 2015 were retrieved from the PubMed, LILACS and SciELO databases following a comprehensive search strategy and using a predetermined set of criteria for article selection.
Results: Five hundred and fourteen studies were identified, of which 21 met the established criteria. Studies in animals have shown anxiolytic and antidepressive effects of ayahuasca, harmine, and harmaline, and experimental studies in humans and mental health assessments of experienced ayahuasca consumers also suggest that ayahuasca is associated with reductions in anxiety and depressive symptoms. A pilot study reported rapid antidepressive effects of a single ayahuasca dose in six patients with recurrent depression.
Conclusion: Considering the need for new drugs that produce fewer adverse effects and are more effective in reducing anxiety and depression symptomatology, the described effects of ayahuasca and its alkaloids should be further investigated.

Keywords: Psychedelic agents; dimethyltryptamine; harmine; monoamine oxidase inhibitors; therapeutic use

Introduction

Ayahuasca is a Quechua name used to describe a pan-Amazonian botanical hallucinogenic beverage produced by boiling the stems of the liana *Banisteriospsis caapi* with the leaves of the shrub *Psychotria viridis*.[1,2] *B. caapi* is rich in β-carbolines such as harmine, tetrahydroharmine (THH), and harmaline, while *P. viridis* contains considerable amounts of the hallucinogenic tryptamine *N,N*-dimethyltryptamine (DMT), a 5-$HT_{1A/2A/2C}$ agonist.[1-5] Pure DMT is not psychoactive after oral administration,[6] but liver and gastrointestinal monoamine oxidase A (MAO-A) inhibition by the β-carbolines in ayahuasca - especially by harmine - allows DMT to reach the systemic circulation and the brain, where it activates 5-$HT_{1A/2A/2C}$ receptors in frontal and paralimbic areas.[5,7,8]

Ayahuasca has been traditionally used by indigenous and mestizo populations of Amazonian countries such as Brazil, Colombia, Peru, and Ecuador for magical-religious and therapeutic purposes.[1,2] However, in the last 25 years, ritual and therapeutic use of ayahuasca has spread from small cities in the Amazonian jungle to the urban centers of South America, United Sates, Europe, Asia, and Africa.[9]

Anecdotal evidence, studies conducted among ayahuasca consumers, and preliminary studies in patients suggest that ayahuasca has broad therapeutic potential, especially for the treatment of substance dependence and anxiety and mood disorders.[10-18] Moreover, pharmacological studies of acute ayahuasca administration to healthy volunteers and mental health assessments of long-term ayahuasca consumers suggest that this compound is relatively safe.[4,5,7,10-15,19-21]

Thus, this study aimed to conduct a systematic literature review of animal and human studies that investigated anxiolytic and antidepressive effects of ayahuasca or of some of its isolated alkaloids (dimethyltryptamine, harmine, THH, and harmaline).

Methods

Data for this systematic review were collected in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA; http://www.prisma-statement.org/usage.htm).

Data acquisition

We attempted to identify all animal and human studies available for review as of 3 April 2015 in which the anxiolytic or antidepressive effects of ayahuasca or of some of its

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isolated alkaloids (dimethyltryptamine, harmine, THH, and harmaline) were analyzed.

Search strategy

The electronic PubMed (1 January 1966 to 3 April 2015), LILACS (1 January 1982 to 3 April 2015), and SciELO (1 January 1998 to 3 April 2015) databases were searched. The following keywords were used: ayahuasca OR dimethyltryptamine OR harmine OR tetrahydroharmine OR harmaline AND anxiety OR anxiogenic OR anxiolytic OR depression OR depressive OR antidepressive OR antidepressant. References were retrieved by searching the aforementioned electronic databases and handsearching of reference lists of the identified literature. All studies published up to 3 April 2015, without language restriction, were included.

Eligibility criteria

The inclusion and exclusion criteria listed below were established prior to the literature search.

Article type. Journal articles, abstracts, letters, conference abstracts, books, and book chapters were included. Case reports, comments, and editorials were excluded.

Study design. The review included (i) animal models of anxiety or depression; (ii) experimental studies of ayahuasca administration to healthy volunteers that assessed anxiety or depressive-like symptoms with validated scales; (iii) observational studies of ayahuasca consumers that assessed anxiety or depressive symptoms with validated scales; and (iv) clinical trials involving patients with a diagnosis of anxiety or depressive disorder based on DSM criteria.

Participants/sample. Rodents (rat or mouse), healthy human volunteer (including ayahuasca consumers), and patients with a diagnosis of anxiety or depressive disorder based on DSM criteria.

Interventions. All designs evaluating the effect of ayahuasca or its alkaloids on anxiety and depressive measures were included.

Comparisons. The main comparators considered were placebo and established pharmacotherapy regimens for anxiety and mood disorders (e.g., imipramine).

Outcomes. Studies investigating the effect of ayahuasca or its alkaloids on anxiety or depressive-like behavioral or biochemical parameters (animal studies) or symptoms (human studies) were included.

Data extraction

All studies were screened by two independent reviewers, with discrepancies resolved by a third reviewer. Names of authors, year of publication, study design (experimental, observational, clinical trial), characteristics of the participants (species, sample size), response criteria (anxiolytic or antidepressive effect), type of intervention (drug, dose), and type of outcome measure (anxiety or depression model or scale) were recorded for all included articles. The sample was divided into (i) animal and (ii) human studies for the sake of clarity and to facilitate interpretation of results.

Results

Study selection

A flow diagram illustrating the different phases of the systematic review is presented in Figure 1.

The literature search yielded 514 separate references. Owing to overlap of coverage between the databases, four of the references were found to be duplicates. A total of 510 citations were reviewed for abstract screening (first pass). Following this pass, 21 potentially relevant references were identified. Full-text reports of these citations were obtained for a more detailed evaluation. Following detailed examination of the reports, all 21 citations were included.

Studies were classified according to the species (animal, human), compound (ayahuasca, DMT, harmine, THH, harmaline), and behavior/symptom (anxiolytic, antidepressive) assessed. The included publications comprised 10 animal studies (two on the anxiolytic effect of harmaline, nine on the antidepressive effect of harmine, and one on the antidepressive effect of ayahuasca) and 11 human studies (three experimental studies, seven observational studies, and one clinical trial).

Animal studies

Anxiolytic effects of harmaline

A study in mice examined the effects of harmaline on state anxiety employing the elevated plus maze test.[22] Lower

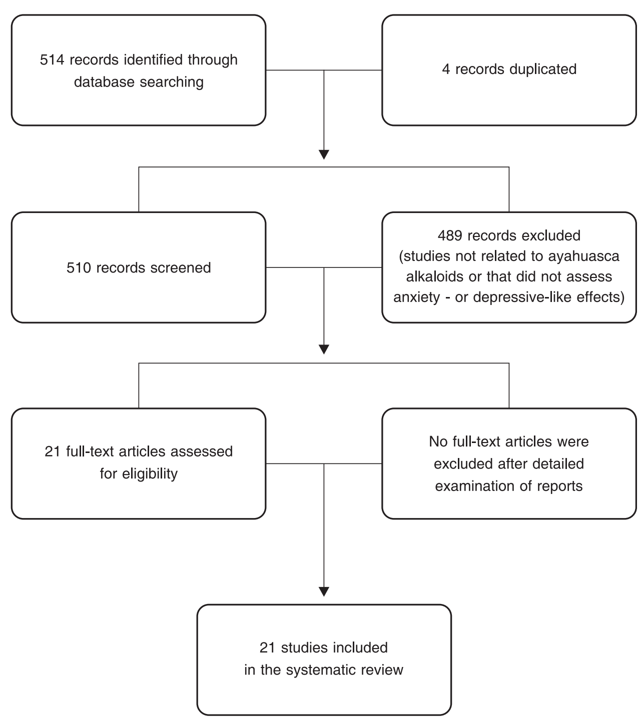

Figure 1 Flow diagram illustrating the different phases of the systematic review.

doses of harmaline (5-10 mg/kg) increased anxiety, while higher doses (20 mg/kg) produced anxiolytic effects. Another study in mice investigated the anxiolytic activity of harmaline using the marble burying test, an animal model of obsessive-compulsive disorder (OCD), and reported that animals treated with 5-7.5 mg/kg harmaline buried a significantly greater number of marbles, which suggests an anxiolytic effect.[23]

Antidepressive effects of harmine

A study in mice using the forced swim test (FST) as an animal model of depression reported that harmine (5-15 mg/kg via intraperitoneal [i.p.] injection) dose-dependently reduced immobility time in this test, which indicates antidepressive effects.[24] These effects were reversed after treatment with a γ-aminobutyric acid ($GABA_A$) receptor antagonist, suggesting involvement of this receptor in the antidepressive effects of harmine.

Since 2009, our group has published several studies describing the antidepressive properties of harmine.[25-30] In the first of these studies, the effects of harmine (5-15 mg/kg) were assessed in rats using the FST.[25] Moreover, hippocampal levels of brain-derived neurotrophic factor (BDNF), an endogenous protein that plays critical roles in neuroplasticity and depression, were assessed in harmine-treated rats. Harmine (10-15 mg/kg) reduced immobility time and increased both climbing and swimming time in rats, which suggests antidepressant effects. Furthermore, harmine (15 mg/kg) increased BDNF levels in the rat hippocampus. A subsequent study assessed the effects of chronic treatment with harmine (5-15 mg/kg/day for 14 days) using the FST in rats.[26] All doses of harmine reduced immobility and increased swimming time. Moreover, harmine at 5-10 mg/kg increased climbing time, whereas the higher doses (10-15 mg/kg) increased BDNF levels in the rat hippocampus.

The antidepressive effects of harmine (15 mg/kg/day for 7 days) were assessed in rats using another animal model of depression, the chronic mild stress (CMS) model.[27] In this study, sweet food consumption, adrenal gland weight, adrenocorticotropic hormone (ACTH), and hippocampal BDNF levels were also assessed. The CMS model induced lower consumption of sweet foods, which is postulated to reflect anhedonia, a core symptom of depressive episodes in humans. Moreover, CMS induced adrenal gland hypertrophy and increased ACTH and BDNF levels. Harmine treatment reversed anhedonia and the increase in adrenal gland weight, and normalized ACTH and BDNF levels. A recent study also used the CMS model and showed that harmine (15 mg/kg/day for 7 days) reversed increased sucrose intake and prefrontal cortex citrate synthase activity in stressed rats.[30]

Considering the involvement of reactive oxygen species (ROS), energy metabolism, and mitochondrial function in the pathophysiology of depression, our group investigated the effects of acute and chronic administration of harmine on several parameters of oxidative stress,[30] mitochondrial function, and cellular energy metabolism,[29,30] For instance, the effects of harmine on lipid and protein oxidation levels (markers of oxidative stress) and on activity of the antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) in the rat brain were evaluated.[29] Acute (5-15 mg/kg) and chronic (5-15 mg/kg/day for 14 days) harmine treatments reduced lipid and protein oxidation in the rat prefrontal cortex and hippocampus, while SOD and CAT activity were increased in the same brain regions.

The effects of harmine on energy metabolism in the rat brain were assessed by evaluation of mitochondrial respiratory chain (complexes I, II, II-III, and IV) and creatine kinase activity.[29] Acute (5-15 mg/kg) treatment with harmine increased creatine kinase activity in the prefrontal cortex (all doses) and striatum (5 mg/kg), while the higher dose (15 mg/kg) decreased creatine kinase in the striatum. Regarding the mitochondrial respiratory chain, harmine increased the activity of complex I in the prefrontal cortex (15 mg/kg) and striatum (10 mg/kg). Chronic treatment with harmine (5-15 mg/kg/day for 14 days) increased creatine kinase in the prefrontal cortex (5 mg/kg) and striatum (5-10 mg/kg), and increased the activity of complex I in the prefrontal cortex (5 mg/kg) and of complex IV in the striatum (10 mg/kg). Acute and chronic treatment with harmine did not alter complex II or II-III activity. These findings suggest that the mechanism of action of the antidepressive effects of harmine may involve, at least in part, activity of creatine kinase and of the mitochondrial respiratory chain, depending on dose and brain area.

As noted previously, a study in rats using the CMS model reported that harmine (15 mg/kg/day for 7 days) reversed the increased activity of citrate synthase, an enzyme involved in mitochondrial function, in the rat prefrontal cortex.[30]

Taken together, these findings support the hypothesis that the antidepressive effects of harmine could be mediated by regulation of cell energy homeostasis, mitochondrial functions, and oxidative stress.

Table 1 shows preclinical evidence of the antidepressive-like effects of harmine in laboratory animals.

Antidepressive effects of ayahuasca

A study in rats showed that orally administered ayahuasca (5 mg/kg) decreased immobility time in the FST. Lower (2.5 mg/kg) and higher doses (10 mg/kg) did not produce significant effects, and the number of dives was not altered by ayahuasca administration.[31]

Human studies

Relaxation and increased positive mood after DMT administration

In an open-label trial involving the intramuscular administration of 0.7 mg/kg DMT to 15 healthy volunteers, 93% of the participants self-reported feelings of relaxation.[32] A double-blind, placebo-controlled, randomized study involving the administration of four doses of intravenous DMT (0.04-0.4 mg/kg) to 15 healthy volunteers reported that non-hallucinogenic doses of DMT (0.05 mg/kg) produced relaxation in some participants.[33] A study that assessed the effects of oral and smoked DMT (25 mg) in six healthy volunteers reported that while oral DMT did not produce

Table 1 Antidepressive-like effects of harmine in animal models

Reference	Model	Animal	Results	Dose
Farzin & Mansouri[24]	FST	Mouse	Reduced immobility	5-15 mg/kg (acute)
Fortunato[25]	FST	Rat	Reduced immobility, increased climbing and swimming, increased BDNF levels in the hippocampus	10-15 mg/kg (acute)
Fortunato[26]	FST	Rat	Reduced immobility, increased climbing and swimming, increased BDNF levels in the hippocampus	5-15 mg/kg/day (14 days)
Fortunato[27]	CMS	Rat	Reversed anhedonia, reduced adrenal gland weight, normalized ACTH and BDNF levels	15 mg/kg/day (7 days)
Réus[28]	Acute and chronic treatment	Rat	Reduced lipid/protein oxidation and increased superoxide dismutase/catalase activity in prefrontal cortex and hippocampus	5-15 mg/kg (acute) 5-15 mg/kg/day (14 days)
Réus[29]	Acute and chronic treatment	Rat	Increased creatine kinase and complex I/IV activity in the prefrontal cortex and striatum	5-15 mg/kg (acute) 5-15 mg/kg/day (14 days)
Abelaira[30]	CMS	Rat	Reversed sucrose intake and prefrontal cortex citrate synthase activity	15 mg/kg/day (7 days)

ACTH = adrenocorticotropic hormone; BDNF = brain-derived neurotrophic factor; CMS = chronic mild stress; FST = forced swim test.

any psychoactive effects, smoked DMT was fully psychoactive and increased positive mood.[6]

Mental health assessments of ayahuasca consumers

In a study among first-time ayahuasca consumers, 28 volunteers were evaluated 1-4 days before and 1-2 weeks after their first participation in an ayahuasca ritual in the *Santo Daime* or *União do Vegetal* religions.[34] Ayahuasca consumption was associated with reduced psychiatric symptoms and increased serenity and tranquility. In a follow-up study performed after 6 months with 23 of the initial 28 volunteers, ayahuasca use was associated with reduced psychiatric symptoms, improved mental health, confidence, and optimism.[35]

One study assessed psychiatric symptoms and neurocognitive functions in 15 experienced (at least 10 years of continuous use) members of the *União do Vegetal* religion, and reported an absence of mental health or cognitive problems.[10] Instead, ayahuasca consumers showed reduced psychopathology, which included a reduction in anxiety and depression symptoms. A reduction in anxiety and depression symptoms was also observed in other studies. In a study which evaluated psychiatric symptoms in 40 adolescent (age 15-19 years) members of the *União do Vegetal* who had consumed ayahuasca at least 24 times in the last 2 years, the ayahuasca-using group had a reduced incidence of anxiety symptoms when compared to a non-ayahuasca-using control group.[36] Moreover, a study with 32 long-term (lifetime 269±314.7 ceremonies; range, 20-1300) North American *Santo Daime* members reported that ayahuasca use was associated with reduced anxiety and depression symptoms.[12] In a study performed among 127 long-term (at least 15 years of continuous use) *Santo Daime* and *Barquinha* members, which included a 1-year follow-up, ayahuasca use was not associated with any psychiatric symptoms, and religion participants showed better neuropsychological performance and reduced psychopathology, including anxiety- and depression-related symptoms.[15]

The effects of ayahuasca on psychometric measures of anxiety, panic-like, and hopelessness were assessed in experienced (at least 10 years of continuous use) *Santo Daime* members during one of their rituals (*Oração*, "prayer"). Questionnaires were administered 1 hour after ayahuasca ingestion in a double-blind, placebo-controlled design. Participants showed reduced panic and hopelessness symptoms after ayahuasca intake, and ayahuasca did not modify state or trait anxiety.[11]

Clinical trials

Our group performed the first clinical trial involving the administration of ayahuasca to patients with recurrent depression.[18] A single dose of ayahuasca was administered to six volunteers with a current depressive episode in an open-label trial conducted in an inpatient psychiatric unit. Ayahuasca administration significantly reduced depressive symptoms from baseline 1, 7, and 21 days after drug intake, according to the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Åsberg Depression Rating Scale (MADRS), and the Anxious-Depression subscale of the Brief Psychiatric Rating Scale (BPRS). These results suggest fast-acting anxiolytic and antidepressant effects of ayahuasca in patients with a depressive disorder.

Discussion

In this systematic review, we identified 21 studies on the anxiolytic and antidepressive effects of ayahuasca and its alkaloids that met our inclusion criteria. Despite the small number of studies and the high degree of heterogeneity among them, the reported results consistently show that these compounds have anxiolytic and antidepressive properties. These findings will be discussed in detail below.

Research performed among ayahuasca consumers over the last 20 years shows that users of this substance do not exhibit symptoms of psychiatric disorders or neurocognitive problems, but instead show normal or better cognitive function, increased well-being and spirituality, and reduced psychopathology, including anxiety and depression symptoms.[10-12,14,15,34-36] Moreover, DMT administration to healthy volunteers suggest that this tryptamine may have anxiolytic properties.[6,32,33]

Studies in rodents have reported that the β-carbolines harmine and harmaline, as well as ayahuasca, produce anxiolytic or antidepressive effects. As harmaline acts as a MAO-A inhibitor,[3,5] the anxiolytic effects of this compound[22,23] could be theoretically explained by an enhancement of serotonin concentrations in the brain after MAO-A inhibition.[37] Nevertheless, the mechanisms of action responsible for the anxiolytic and antidepressive properties of harmine and harmaline are not completely understood, and other non-serotonergic mechanisms could also be involved.

Specifically, the antidepressive effects of harmine are apparently independent of its effects as a MAO-A inhibitor,[3,5] and seem to be mediated by regulation of cell energy homeostasis, mitochondrial functions and oxidative stress,[28-30] and modulation of BDNF, an endogenous protein involved in neuroplasticity and depressive symptoms.[25-27] Harmine and harmaline also bind to 5-HT_{2A} receptors.[38-40] Since hallucinogens increase cortical glutamate levels following activation of 5-HT_{2A} receptors, increasing the expression of BDNF in prefrontal areas,[41-43] the agonist action of harmine and harmaline in this serotonergic receptor could also lead to increased BDNF levels.[25-27]

A study suggested that the $GABA_A$ receptor could be involved in the antidepressive effects of harmine.[24] Nevertheless, some studies suggest that harmine, harmaline, and THH display little affinity for benzodiazepine receptors.[38,39]

Regarding DMT, there is evidence that $5\text{-HT}_{1A/2A/2C}$ receptor agonists modulate emotional processing, reduce anxiety and depressive symptoms, and increase positive mood. Interestingly, cortical expression of $5\text{-HT}_{1A/2A/2C}$ receptor is altered in post-mortem samples of depressed patients.[43] Therapeutic drugs that are 5-HT_{1A} receptor agonists produce anxiolytic and antidepressive effects in animals and humans,[37,43,44] and $5\text{-HT}_{2A/2C}$ receptor agonists produce anxiolytic and antidepressive effects in animals.[45-47] Moreover, there is increasing evidence that anxiety and depressive symptoms are associated with inflammatory processes, and $5\text{-HT}_{1A/2A/2C}$ receptor agonists have anti-inflammatory properties.[43,48-50]

Other $5\text{-HT}_{1A/2A/2C}$ receptor agonists, such as psilocybin and lysergic acid diethylamide (LSD), also produce reductions in anxiety and depressive symptoms and increases in positive mood. In the mid-1950s and 1960s, several studies investigated the potential therapeutic use of psilocybin and LSD in the treatment of disorders such as neurosis and OCDs, and as an adjunctive therapy in the terminally ill.[42,51-56] However, a definite conclusion regarding the potential beneficial effects of these compounds cannot be drawn from previous investigations, since many of these studies had important methodological limitations, such as lack of a control group or randomization, absence of double-blind/placebo-controlled designs, and limited follow-up data.[42,51-56]

Recent studies reported that psilocybin produces anxiolytic effects in mice in the marble burying test, an animal model of OCD,[57] and that LSD produced antidepressive-like effects and normalized learning behavior and hippocampal serotonin 5-HT_2 signaling in a rat model of depression (olfactory bulbectomy).[58]

As previously reported, smoked DMT increased positive mood in healthy voluntters,[6] and both psilocybin[59-63] and LSD[64] also increased positive mood in experimental studies in humans. Case reports[56,65-68] and clinical trials[69] suggest that psilocybin and LSD may be beneficial for patients with OCD. Moreover, psilocybin- and LSD-assisted psychotherapy has been shown to reduce anxiety and depressive-like symptoms in patients with anxiety and depression associated with life-threatening diseases such as advanced-stage cancer.[70-72]

The antidepressive properties of ayahuasca could also be related to alterations of cortical connectivity in the default mode network (DMN), a group of brain areas involved in introspection, meditative states, daydreaming, imagination, and mind-wandering. Depressive states are associated with increased rumination, a self-referential process that may become difficult to disengage and is associated with increased activity of the DMN, and acute ayahuasca administration (2.2 mL/kg of body weight) significantly reduced DMN activation.[73] A recent study evaluated cortical thickness in 22 regular users of ayahuasca (average 5.3 years of continuous use; range: 2-13 years) using magnetic resonance imaging (MRI) and reported significant cortical thinning in the posterior cingulate cortex (PCC), a key node of the DMN.[74]

Regarding other serotonergic hallucinogens, a recent functional MRI (fMRI) study involving intravenous administration of psilocybin (2 mg) to 15 healthy volunteers reported significant decreased cerebral blood flow in several brain areas including the PCC and the medial prefrontal cortex (mPFC), another important component of the DMN.[75] A subsequent study reported increased functional connectivity of the DMN and the task-positive network (TPN), involved in goal-directed attentional tasks.[76] Since the DMN and TPN have opposite functions, the authors suggested that the subjective effects of hallucinogens, as well as psychotic and meditative states, could be caused by disruption of DMN-TPN functional connectivity. This disruption would obfuscate the separateness of internally and externally focused states, profoundly altering cognition, perceptions, emotions, and consciousness. However, no significant change was observed in DMN-TPN connectivity after acute ayahuasca administration. Thus, further studies are needed to better explore the subjective and therapeutic effects of serotonergic hallucinogens.

Animal and human studies suggest that ayahuasca and its alkaloids can produce anxiolytic and antidepressive effects, which are probably mediated by agonist action on $5\text{-HT}_{1A/2A/2C}$ receptors. These receptors are involved in emotional processing, regulation of BDNF brain levels, anti-inflammatory actions, and altered DMN functional connectivity. However, the mechanisms of action involved in these therapeutic effects are not completely understood, and, at least in the case of harmine, may include non-serotonergic mechanisms that regulate cell energy homeostasis, mitochondrial functions, and oxidative stress.

Considering that the average time necessary for the onset of therapeutic action of commercially available antidepressants is 2 weeks,[77] the fast antidepressant action of ayahuasca reported in our preliminary clinical trial is promising. Recently, our group increased the number of depressive patients receiving ayahuasca treatment and used single photon emission computed tomography (SPECT) to assess regional cerebral blood flow after drug administration. Our results suggest similar positive effects as described in our pilot study.[78]

In summary, the results of this systematic review suggest that ayahuasca and its alkaloids have anxiolytic and antidepressive properties. These results are supported by studies using rodent models of anxiety and depressive disorders, experimental studies in healthy volunteers, observational studies in ayahuasca consumers, and preliminary data from depressed patients.

Investigation of these compounds could provide new pharmacological treatments with fast-acting beneficial effects for patients with anxiety and depressive disorders. Further studies are needed to replicate these findings.

Limitations of the present review include the small number of studies, especially clinical trials, and the heterogeneity among reviewed reports. Furthermore, most evidence showing anxiolytic and antidepressive effects of ayahuasca or its alkaloids comes from rodent studies. Thus, it is premature to extrapolate these results to humans until more research is conducted.

With the exception of a single pilot study, the human studies included in this review were mostly experimental and observational in nature. The experimental studies described had small sample sizes and were not designed to assess anxiolytic or antidepressive effect. An important limitation of observational studies with long-term ayahuasca consumers is that it is generally very hard to differentiate whether the improvements described are a consequence of the ingestion of ayahuasca or of joining a religious group, which can improve quality of life and well-being.[79] Experimental and observational studies provide weak evidence of causality, and until more clinical trials are developed, the available evidence in humans must be considered preliminary.

Despite these limitations, the results showing anxiolytic and antidepressive effects of ayahuasca and its alkaloids are relatively constant, and have been reported in rodents, healthy volunteers, and depressed patients.

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Disclosure

The authors report no conflicts of interest.

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