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ORIGINAL ARTICLE

Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report

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Objectives: Ayahuasca (AYA), a natural psychedelic brew prepared from Amazonian plants and rich in dimethyltryptamine (DMT) and harmine, causes effects of subjective well-being and may therefore have antidepressant actions. This study sought to evaluate the effects of a single dose of AYA in six volunteers with a current depressive episode.
Methods: Open-label trial conducted in an inpatient psychiatric unit.
Results: Statistically significant reductions of up to 82% in depressive scores were observed between baseline and 1, 7, and 21 days after AYA administration, as measured on 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). AYA administration resulted in nonsignificant changes in Young Mania Rating Scale (YMRS) scores and in the thinking disorder subscale of the BPRS, suggesting that AYA does not induce episodes of mania and/or hypomania in patients with mood disorders and that modifications in thought content, which could indicate psychedelic effects, are not essential for mood improvement.
Conclusions: These results suggest that AYA has fast-acting anxiolytic and antidepressant effects in patients with a depressive disorder.

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

Introduction

Depression is a highly prevalent disorder and is associated with intense personal suffering, increased mortality, and high morbidity.[1,2] Although its etiology is unknown, some theories suggest that biological factors may be implicated.[3] One such theory is the monoamine hypothesis, which suggests that an imbalance in cerebral monoamines such as dopamine, norepinephrine, and, especially, serotonin is responsible for depressive symptomatology.[3] The monoamine hypothesis is the theory on which the leading commercially available antidepressants are based.[3]

Currently available treatments have limitations that can lead to low therapeutic effectiveness, especially related to low response rates, as well as adverse effects and latency to onset of therapeutic action.[3] Thus, new interventions, particularly those that with the potential for acute effect, would have a huge impact on the treatment of depression. The *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine, for example, has rapid and potent antidepressant effects in treatment-resistant major depressive disorder (MDD) and bipolar depression, and its use is considered one of the most exciting areas in contemporary psychiatric research.[4,5]

Ayahuasca (AYA), a botanical hallucinogen traditionally used by indigenous groups of the Northwest Amazon region for ritual and medicinal purposes,[6,7] is a potential candidate for this new generation of antidepressant research focusing on new pharmacological treatments that produce immediate and more pronounced effects. AYA is prepared by prolonged decoction of the bark of the vine *Banisteriopsis caapi* with the leaves of the shrub *Psychotria viridis*.[6,7] *B. caapi* contains the β-carboline alkaloids harmine, tetrahydroharmine (THH), and harmaline, which act as monoamine oxidase A inhibitors

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(MAOI), while *P. viridis* is rich in the psychedelic tryptamine *N, N*-dimethyltryptamine (DMT).[6,8-11]

The psychoactive effects of AYA are produced by a combined action of peripheral (gastrointestinal and liver) monoamine oxidase A (MAO-A) inhibition by harmine and central 5-$HT_{1A/2A/2C}$ agonist action of DMT on frontal and paralimbic brain areas.[8,9,12] Studies conducted among long-term (i.e., years or decades) members of religious groups that use AYA ritually suggest that this population does not present evidence of psychological, neuropsychological, or psychiatric harm caused by AYA.[13-15] In fact, there are several reports describing reduced mental health problems in AYA users.[13-15] Nevertheless, given the small number of studies, most with a limited number of participants, there is insufficient information to allow a definitive conclusion on this topic, and more studies on the potential long-term toxicity of AYA are required.

An increasing number of studies report antidepressive potential for AYA alkaloids in animals.[16-24] Furthermore, a double-blind, placebo-controlled animal study reported reduced hopelessness and panic-related signs after acute AYA administration,[25] and preliminary data in humans also support an antidepressive action for AYA.[26]

The agonist action of AYA alkaloids on serotonergic receptors and its inhibitory effects on MAO-A, associated with field and laboratory evidence suggesting that AYA causes a sensation of well-being, led to the hypothesis that this substance could be useful in the treatment of depression in humans. Thus, the objective of the present preliminary, open-label study was to evaluate the acute effects of a single dose of AYA in patients diagnosed with depression and to test whether AYA administration could produce an acute antidepressant effect.

Methods

Volunteers

Six volunteers (two men and four women, mean age 44.16±13.55 years) with a diagnosis of recurrent MDD participated in the study. Within this group, two volunteers were experiencing a current mild depressive episode, three were experiencing a moderate episode, and one was experiencing a severe depressive episode. None of the volunteers were experiencing depressive episodes with psychotic symptoms.

Participants were recruited through local advertisements and by referrals from private psychiatric clinics. Volunteers were not taking any psychopharmaceuticals at the time of recruitment; they were patients that did not exhibit a significant therapeutic response to their latest medication and were in the process of switching to a new agent. Patients participated in the study before the introduction of the new medication.

None of the participants had ever used illicit drugs or AYA, as assessed by a medical interview, and had no evidence of current clinical conditions or pregnancy, as assessed by medical interview, physical examination, and laboratory tests. A diagnosis of bipolar disorder and a previous history of mania or hypomania induced by antidepressants/substance use were considered exclusion criteria.

The study was conducted in accordance with the Declarations of Helsinki and Tokyo concerning human subject research and approved by the Research Ethics Committee of Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, Ribeirão Preto, state of São Paulo, Brazil (HC-RP process no. 2484/2008). The volunteers received detailed information on the nature of AYA, the general psychological effects of hallucinogens, and its possible adverse effects, as reported in the psychiatric literature. All volunteers gave their written informed consent to participate.

Drug

We obtained a standard sample of AYA prepared by members of the Santo Daime community, consisting of the stalks of *B. caapi* (rich in harmine, THH, and harmaline) combined with the washed leaves of *P. viridis* (rich in DMT), boiled and concentrated for several hours. The resulting brew was stored in plastic bottles at room temperature at the Santo Daime community and subsequently in a refrigerator in the Department of Neurosciences and Behavior, Ribeirão Preto Medical School, Universidade de São Paulo, Ribeirão Preto, Brazil. AYA was stored under refrigeration until the day of the experimental session. All AYA used in the present study was from this original batch.

Each subject drank 120-200 mL of AYA (2.2 mL/kg body weight). The AYA batch used in the experiment contained 0.8 mg/mL DMT, 0.21 mg/mL harmine, and no harmaline at the chromatography detection threshold of 0.02 mg/mL. To quantify the content of each alkaloid, a 1-mL sample of AYA was homogenized with sodium acetate buffer solution (pH = 9), extracted with 5 mL diethyl ether in a shaker (20 min), and centrifuged at 3,000 rpm for 15 min. The organic phase was collected and evaporated under a nitrogen stream. The residue was dissolved in 1 mL methanol and 1 μL of the resulting solution was analyzed by gas chromatography/mass spectrometry (GC/MS), performed using a Varian CP3800 gas chromatograph coupled to a Varian Saturn 2000 ion trap mass spectrometer (Varian Inc.). A capillary column (DB-5MS, 30 m × 0.25 mm i.d. × 0.25 μm film thickness; Agilent) was used. The chromatographic conditions were as follows: injector temperature 250°C in splitless mode and oven temperature program 80°C for 1 min, ramped at 5°C/min to 220°C and held for 10 min, and then to 300°C for 5 min. Helium at a flow rate of 0.8 mL/min was used as carrier gas.

Medical interview and laboratory tests

A general clinical examination; a laboratory workup consisting of a complete blood cell count; evaluation of blood glucose levels; measurement of plasma sodium and potassium, urea, creatinine, urinary beta-HCG (in women of childbearing age), bilirubin, and liver enzymes; and an electrocardiogram were performed.

Psychometric instruments

Structured Clinical Interview for DSM-IV (SCID-IV)

This interview was used to assess whether potential patients met the inclusion and exclusion criteria.[27,28]

Brief Psychiatric Rating Scale (BPRS)

This clinician-administered scale was used to evaluate four symptom dimensions: 1) Withdrawal-Retardation; 2) Thinking Disorder; 3) Anxious-Depression; and 4) Activation.[29,30]

Young Mania Rating Scale (YMRS)

This clinician-administered scale was used to assess manic symptoms.[31,32]

Hamilton Rating Scale for Depression (HAM-D)

This clinician-administered scale was used to assess and quantify depressive symptoms in patients with a previous diagnosis of mood disorder.[33,34]

Montgomery-Åsberg Depression Rating Scale (MADRS)

This clinician-administered scale was used to assess the severity of depressive symptoms.[34,35]

Assessment of tolerability

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at the following time points: 10 minutes (-10) before AYA administration (baseline) and 40 min (+40), 80 min (+80), 140 min (+140), and 180 min (+180) after AYA administration. Blood pressure was measured using a mercury sphygmomanometer (Becton Dickinson, Brazil).

Adverse effects were not systematically assessed. Dysphoric effects were recorded by means of spontaneous verbal reports.

Experimental procedure

Volunteers were admitted to an inpatient psychiatric unit for 2 weeks prior to AYA administration as part of an open-label trial. During this time, volunteers were not under the influence of any psychiatric medication or recreational drugs. The experimental session, which was performed individually, lasted on average 4 h and consisted of AYA intake followed by administration of the scales. During measurements, volunteers remained seated in a comfortable recliner in a quiet, dimly lit room. After the end of the session, patients remained under observation for 24 h; if no complications were observed, they were discharged.

The BPRS, YMRS, HAM-D and MADRS scales were completed by a psychiatrist with clinical experience and training in the use of these scales, at the following time points: 10 minutes (-10) before AYA administration (baseline); 40 min (+40), 80 min (+80), 140 min (+140), and 180 min (+180) after AYA administration; and on days 1 (D1), 7 (D7), 14 (D14), and 21 (D21) after AYA administration.

Data analysis

After verification of data distribution, descriptive statistics and repeated-measures analysis of variance (ANOVA) were used for statistical analysis. Significance was set at $p < 0.05$.

Results

The clinical and demographic characteristics of the study participants are presented in Table 1.

Regarding depressive symptoms, the average baseline HAM-D score of the volunteers was 17.56 ± 7.73, which was classified according to the scale guidelines as a moderate level of depression. At D1, there was a 62% decrease in the mean score, which was statistically significant ($p = 0.01$) (Figures 1 and 2). This decrease was even more pronounced by D7 (72%, $p = 0.01$). However, on D14, the level of symptoms increased, and although the symptom score remained 45% below baseline, this difference was not statistically significant ($p = 0.11$). On D21, there was a further significant decrease in depressive symptoms ($p = 0.01$). The greatest score changes were observed for items related to depressed mood, feelings of guilt, suicidal ideation, and difficulties at work/activities, i.e., those associated with typical depressive symptoms.

Regarding MADRS scores, results were similar to those observed for the HAM-D scale. The average baseline score of the volunteers was 23.5 ± 11.14 points. At +180, there was a significant decrease in MADRS scores (38%, $p = 0.01$) (Figures 1 and 3). On D1, a more robust decrease was observed ($p = 0.003$), and the average score on D7 was 82% below baseline ($p = 0.009$). On D14, a significant increase in symptoms was observed ($p = 0.001$), although a subsequent significant decrease occurred on D21 ($p = 0.002$). As observed with the HAM-D scale, the most significant score changes were observed for items related to apparent and

Table 1 Clinical and demographic characteristics of patients with recurrent major depressive disorder (n=6)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)/sex	47/female	61/female	28/female	58/male	31/female	36/male
Severity of current depressive episode	Moderate	Mild	Severe	Mild	Moderate	Moderate
HAM-D score	16	11	29	7	20	20
MADRS score	18	16	39	9	27	32

HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Åsberg Depression Rating Scale.

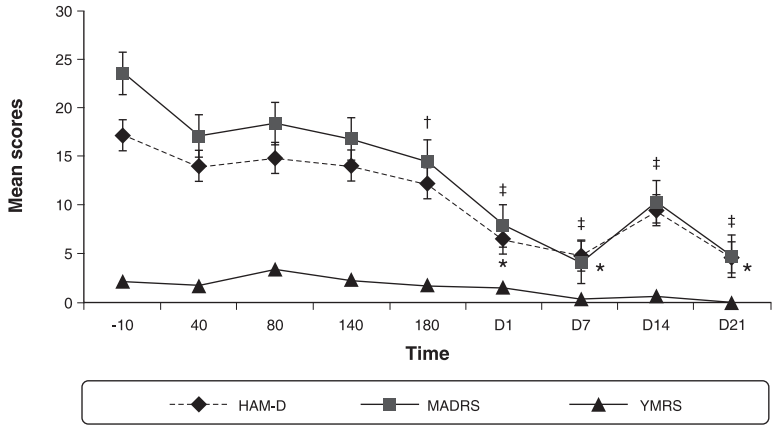

Figure 1 Temporal distribution of scores (means from six volunteers) on the Hamilton Rating Scale for Depression (HAM-D), Montgomery-Åsberg Depression Rating Scale (MADRS), and Young Mania Rating Scale (YMRS). HAM-D: * $p < 0.05$; MADRS: † $p < 0.05$, ‡ $p < 0.01$. Error bars denote one standard error of the mean.

expressed sadness, pessimistic thinking, suicidal ideation, and difficulty concentrating.

Regarding the BPRS scale, volunteers were generally asymptomatic on the withdrawal-retardation (BPRS-WR), thinking disorder (BPRS-TD), and activation (BPRS-A) subscales at baseline (Figure 4). AYA administration produced nonsignificant increases in the scores of these subscales, with effect peaking at 80 min. After this time point, scores decreased and returned to baseline at 180 min. Generally, the symptoms expressed referred to disorientation/confusion, conceptual disorganization, psychomotor retardation, and emotional withdrawal. Although nonsignificant, the increase in the scores of these subscales at 80 min after AYA administration suggests that AYA produced mild psychoactive effects.

On the Anxious-Depression BPRS subscale (BPRS-AD), volunteers demonstrated higher scores at baseline, likely due to the presence of depressed mood, feelings of guilt, and psychic anxiety, which are typical symptoms of the underlying psychopathology. Throughout the experiment, the presence of these symptoms varied, but values remained lower as compared to baseline. At +140, these symptoms were significantly reduced ($p = 0.02$) and remained so (72% below baseline) until D7, when they began to increase but still remained significantly lower than baseline values (Figure 4).

Regarding the YMRS scale, volunteers exhibited no significant changes in symptoms throughout the experiment (Figure 1). However, irritability and decreased capacity for insight and sleep were more prevalent during the first 80 minutes following AYA administration, which was likely associated with the peak period of the subjective effects of AYA.

AYA was well tolerated by all patients. With the exception of vomiting, volunteers did not spontaneously report any other adverse effect. Volunteers considered the effects of AYA on thought content and sensory perception mild and short-lived, and none reported dysphoric manifestations associated with the psychoactive effects of AYA. Blood pressure increased moderately and nonsignificantly (Table 2).

Vomiting was reported by 50% of the volunteers. However, patients were informed before the experimental session that AYA could induce vomiting, and this emetic

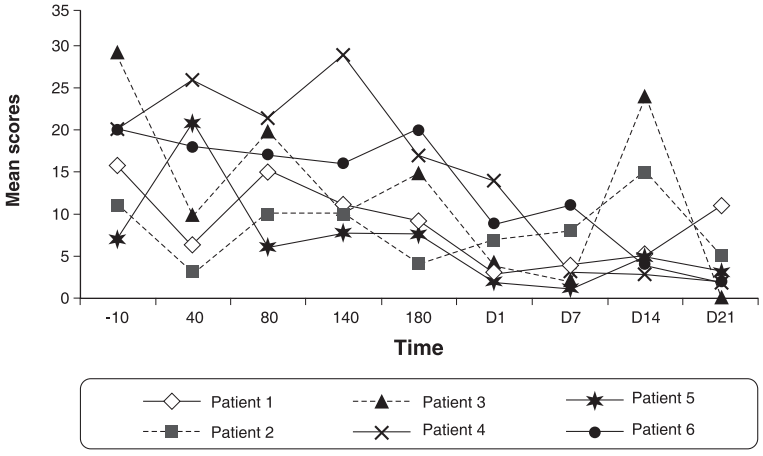

Figure 2 Temporal distribution of individual scores on the Hamilton Rating Scale for Depression (HAM-D) (n=6).

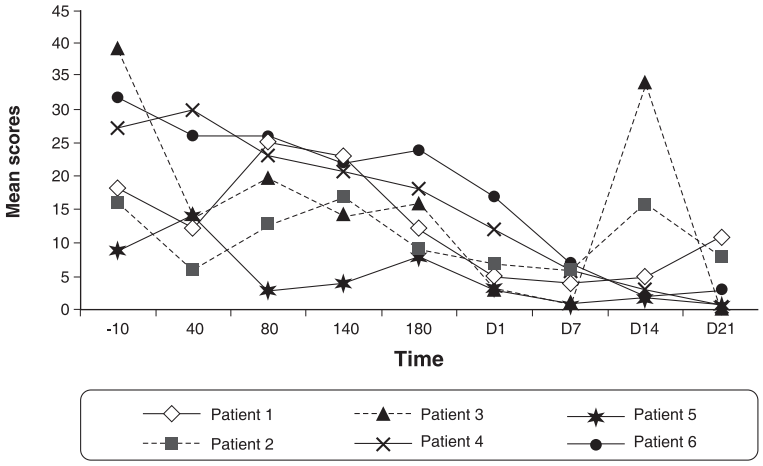

Figure 3 Temporal distribution of individual scores on the Montgomery-Åsberg Depression Rating Scale (MADRS) (n=6).

effect was considered by patients as an integral part of the effects produced by AYA. Patients did not consider vomiting as causing severe discomfort.

Discussion

The results of the present investigation demonstrate that AYA has significant and quite impressive acute antidepressive effects. Score reductions were observed in both the HAM-D and MADRS scales on D1 and D7, and these effects lasted for several days. It is noteworthy that these changes showed a profile that was very similar across volunteers, regardless of the prior level of depression, i.e., the severity of the current depressive episode. The antidepressant potential of AYA was previously demonstrated in a study that reported a decrease in hopelessness symptoms after acute AYA intake.[25]

The average time necessary for the onset of therapeutic action of commercially available antidepressants is 2 weeks.[3] Considering currently available medications, the fast antidepressant action of AYA is promising, as it may provide faster reductions in depressive symptoms. Moreover, the antidepressant effects of AYA alkaloids may inspire a new area of depression research.

Interestingly, symptoms increased on D14 as measured by the HAM-D and MADRS scales, although a subsequent significant decrease occurred on D21 in both scales. Although increased, HAM-D scores still remained 45% below baseline values, but this difference was nonsignificant. On the other hand, MADRS scores on D14 were significantly increased.

The decreases and increases in depressive symptoms after AYA administration could reflect complex intracellular events that remain active after the acute effects of AYA have subsided. The acute antidepressive effects of ketamine, for instance, may be sustained for weeks to months and are associated with increased synaptogenesis and spine formation, which seem to be related with increases in brain-derived neurotrophic factor (BDNF) protein levels.[4,5] Studies conducted in rodents by our group and by others using doses of 10-15 mg/kg harmine have demonstrated antidepressive effects for this compound, which were associated with increases in BDNF levels.[17,19,21]

Furthermore, harmine, THH, and harmaline are potent natural, selective, reversible, and competitive inhibitors of

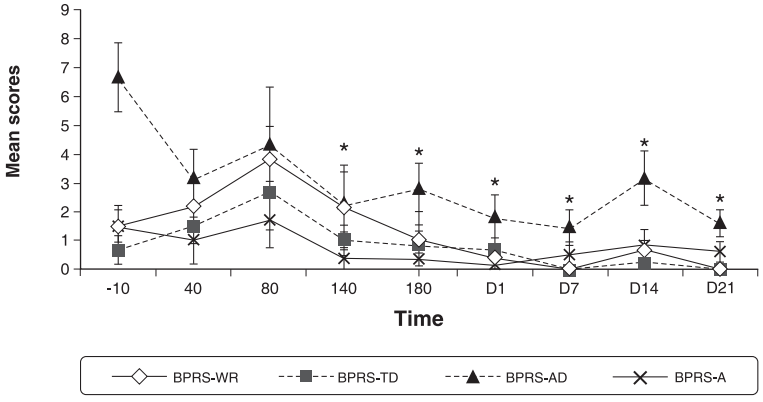

Figure 4 Temporal distribution of scores (means from six volunteers) on the Brief Psychiatric Rating Scale (BPRS) subscales (WR = Withdrawal-Retardation; TD = Thinking Disorder; AD = Anxious-Depression; and A = Activation). * $p < 0.05$. Error bars denote one standard error of the mean.

Table 2 Systolic/diastolic blood pressure measurements in patients with recurrent major depressive disorder (n=5)*

	Mean ± SD	Median	Minimum	Maximum
SBP (baseline)	118±14.83	120	100	140
SBP (140 min)	119±23.02	120	85	150
DBP (baseline)	79.4±9.31	80	70	90
DBP (140 min)	76.4±13.74	80	60	90
HR (baseline)	78±11.48	78	68	96
HR (140 min)	72.2±7.69	70	64	84

DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure; SD = standard deviation.
* Data missing for one patient.
The 140-min time point was chosen because the subjective effects of AYA peak around this time, as do DMT plasma levels.[8-12] All blood pressure values expressed in mmHg. HR values expressed in beats per minute.

the MAO enzyme, especially of the MAO-A subtype.[9,36] THH acts as a selective serotonin reuptake inhibitor as well as an MAOI.[9,37] Inhibition of both systems – MAO and serotonin reuptake – may result in elevated levels of brain serotonin and other monoamines, producing antidepressant effects.[9,25,38]

The statistically significant reductions in BPRS-AD scores from D1 to D21 suggest that AYA produced antidepressive and anxiolytic effects. A previous study reported decreased panic-related signs after acute AYA intake.[25]

AYA administration did not produce statistically significant sensory, cognitive, or affective modifications as assessed by the BPRS and YMRS scales. Although nonsignificant, in the present study these effects were observed during a period ranging from 80 to 140 min after AYA administration, which is the time point when the subjective effects of AYA are peaking, as are DMT plasma levels.[8-12]

The absence of statistically significant effects on BPRS-TD scores could be explained by the DMT concentration found in our AYA batch (0.08 mg/mL), which is lower than DMT doses used in previous studies that reported significant psychotropic effects of AYA (0.53 mg/mL DMT).[9,12] The nonsignificant effects of AYA on the BPRS-TD subscale suggest that changes in sensory perception and thought content may not be essential for therapeutic effects.

AYA was well tolerated by all patients, suggesting that it can be safely administered to depressed patients. This result corroborates previous studies reporting a good tolerability profile for AYA administration to healthy volunteers.[8-12,15,25,39] In the present study, the psychoactive effects of AYA were considered by participants as mild and short-lived, corroborating the nonsignificant effect of AYA on the BPRS-TD subscale. The nonsignificant increases in blood pressure replicate previous findings in human studies suggesting that AYA produces moderate cardiovascular effects.[8-12,15,25,39]

Early academic research on classical hallucinogens was designed considering the powerful influences of set (psychological state) and setting (environment) on the effects of this class of substances.[40] Considering this background, in the present study volunteers were kept as comfortable as possible, remaining seated in a recliner in a quiet, dimly lit room throughout the experimental session. Investigator interference was minimal, allowing patients to concentrate on the effects of AYA. This safe environment may have reduced the probability of dysphoric reactions.[40]

Vomiting was the only adverse effect reported by volunteers (50%). Patients were informed before the experimental session that vomiting was a possible effect of AYA, as nausea and vomiting are the most frequently reported adverse effects in clinical trials of acute AYA administration.[8-12,15,39] In the present study, vomiting apparently did not have a significant influence on the antidepressive effects of AYA. Patients did not consider this emetic effect to be a severe discomfort, a result that is in line with previous studies of acute AYA administration to healthy volunteers, which reported that most participants regarded their AYA experience as pleasant despite the occurrence of vomiting.[8-12,15,39]

In future studies, it would be interesting to try to reduce the emetic effect of AYA by premedicating with an antiemetic. However, this possibility should be explored with caution, considering that AYA alkaloids could interact with antiemetic drugs. Another possibility could be to administer AYA in different formulations. Freeze-dried AYA appears to produce less vomiting than oral AYA.[8,11,15,39] Interestingly, variable degrees of nausea, vomiting, and, occasionally, simultaneous diarrhea are common in AYA rituals. In these contexts, however, these purgative effects are considered positive and cleansing.[7]

Important limitations of the present open-label study include the small sample size, the absence of a systematic inquiry about side effects, and the lack of placebo and control groups. Although patients did not spontaneously report adverse effects other than vomiting, the lack of a systematic assessment of adverse effects may have reduced the likelihood of registering more subtle effects, such as impacts on cognition. Future studies should assess the possible adverse effects of AYA in clinical populations by using other subjective measures, such as visual analogue scales and other scales that measure hallucinogenic effects, and by exploring other variables that could be modified by AYA administration as reported in previous studies, such as neuropsychological, neurophysiological, autonomic, neuroendocrine, and immunological parameters.[8,10,11,14,15]

Ideally, future studies involving AYA and depressed patients or other clinical populations should also be designed to include a control group. This group could receive a placebo, a comparator drug with an established therapeutic indication, or AYA preceded by pretreatment with a 5-HT_{2A} receptor antagonist to investigate possible

mechanisms of action. Regarding the small number of patients, additional studies with larger sample sizes and using neuroimaging techniques (single photon emission tomography, SPECT) are underway in our laboratory.

The aforementioned limitations should be considered taking into account the novelty of this research and its preliminary nature. To our knowledge, the use of AYA in a controlled clinical setting in patients with current depression – or in any other clinical population – has never been investigated. Moreover, the results of the present study, although preliminary, are corroborated by mounting research showing antidepressive potentials for AYA alkaloids in nonhuman animals[16-24] and in humans.[13,25,26]

Finally, the reported results may prompt novel research into substances with faster therapeutic actions than currently available pharmacological resources, thus making antidepressive treatment more effective.

The findings of this preliminary study demonstrate the potential antidepressant and anxiolytic effects of AYA, effects that, importantly, have an earlier onset of action when compared to traditional antidepressants. These findings suggest that AYA may represent a powerful new substance for the treatment of depressive and anxiety symptoms. However, these results deserve careful analysis, given the inherent limitations of an uncontrolled, open-label study with a small sample size. Other studies are needed to replicate these preliminary observations and to test, for example, the most effective dose (or doses) of AYA and the safety, tolerability, and effectiveness of AYA administration over a longer period of time.

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Disclosure

The authors report no conflicts of interest.

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