Metabolic Brain Disease (2025) 40:220
https://doi.org/10.1007/s11011-025-01650-6

RESEARCH

Immunomodulatory and behavioral effects of ayahuasca and N, N-dimethyltryptamine in a rat model of lipopolysaccharide-induced depression

Daniel do Nascimento Sousa[1] · Monique de Azevedo[2] · Maria Lucília Santos[3] · Tatiana Karla dos Santos Borges[4] · Daniela Mara de Oliveira[2] · Eloisa Dutra Caldas[1]

Received: 14 April 2025 / Accepted: 30 May 2025

Abstract

Ayahuasca (Aya) is an Amazonian beverage traditionally used as medicine by Indigenous people in South America to treat various illnesses and have shown a potential to treat depression. This study aimed to investigate the antidepressant effects of fluoxetine, Aya and N, N dimethyl tryptamine (DMT), a component of the beverage, focusing on the modulation of inflammatory serum cytokine profiles and behavior of Wistar rats subjected to lipopolysaccharide (LPS)-induced depression. In total, 126 rats were randomly assigned to seven groups: saline control, LPS, fluoxetine, three ayahuasca groups (dosed at 0.5, 1, and 2 times the usual ritualistic dose, Aya0.5, Aya1 and Aya2), and one DMT treatment group. The rats received LPS every other day from day 1 to 13 and fluoxetine, Aya and DMT daily from day 2 to 14. At day 15, the rats were submitted to open field and forced swimming tests, plasma samples were collected and the animals were euthanized. The LPS group showed lower body weight grain and higher plasma levels of pro-inflammatory cytokines IL-1α ($p<0.001$), TNF-α, and IL-12p70 compared to control, which were significantly reduced by the treatment groups ($p<0.05$ up to $p<0.0001$), indicating a potential for modulation of the inflammatory state seen in depression. The Aya2 group exhibited increased locomotion in the open field arena compared to the fluoxetine ($p<0.05$) and DMT ($p<0.01$) groups, with a significantly higher percentage of entries into the center than the control group ($p<0.01$). Furthermore, treatments with fluoxetine, Aya, and DMT significantly increased swimming time compared to the LPS group ($p<0.01$), and fluoxetine and the Aya0.5 groups displayed higher climbing times compared to LPS and control ($p<0.05$). Although the LPS model did not consistently induce depressive-like behaviors, the results highlight the potential of ayahuasca and DMT to modulate the immune system and reduce pro-inflammatory cytokine levels associated with depression, which could have significant implications for treating inflammation-related aspects of depression.

Highlights

- LPS-treated Wistar rats received ayahuasca (Aya), fluoxetine or DMT for 13 days.
- LPS decreased body weight and increased the levels of IL-1α, which was reverted by treatment groups.
- Locomotion and entries into the center of the open field were higher in the Aya2 group.
- Aya, and DMT increased swimming time in the forced swimming test (FST) compared to LPS.
- Fluoxetine and Aya0.5 showed higher climbing times in the FST.

Keywords Depression · Ayahuasca · DMT · LPS-induced depressive rats · Behavior · Cytokines

✉ Eloisa Dutra Caldas
eloisa@unb.br

[1] Laboratory of Toxicology, Department of Pharmacy, Faculty of Health Sciences, University of Brasília, Brasilia, DF, Brazil

[2] Department of Genetics and Morphology, Institute of Biological Sciences, University of Brasília, Brasilia, DF, Brazil

[3] Chemistry Institute, University of Brasília, Brasilia, DF, Brazil

[4] Laboratory of Cellular Immunology, Pathology Area, Faculty of Medicine, University of Brasilia, Brasilia, DF, Brazil

Published online: 11 June 2025

Introduction

Depression is a widespread neuropsychiatric disorder affecting millions worldwide, leading to functional limitations and reduced quality of life (Herman et al. 2017). Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is a commonly used drug for the treatment of depression (Rossi et al. 2004). However, SSRIs are limited by a delayed response of 2 to 4 weeks, high dropout rates, and a low response rate (Rossi et al. 2004; Cuijpers et al. 2023), limitations that are also reported for other antidepressants (Bollini et al. 1999). This context highlights the interest in exploring new, fast-acting, efficient, and well-tolerated antidepressants to address gaps in current clinical depression treatment.

Ayahuasca, the "vine of the souls" in the Quechua language, is an Amazonian beverage traditionally used for religious and medical purposes by Indigenous people (Rivier and Lindgren 1972). Luna (1984) described the medicinal use of ayahuasca by Peruvian shamans (called "doctor" or plant-teachers) to cure themselves or learn through visions how to treat other people with various ailments, and to help deal with emotional distress. In the 20 th century, ayahuasca-based Christian religious groups were formed in Brazil, such as *União do Vegetal* and *Santo Daime*, which later expanded to other countries (Labate and Feeney 2012). The brew is generally prepared with *Psychotria viridis* Ruiz & Pav. and *Banisteriopsis caapi* (Spruce ex Griseb.) C.V. Morton (Freedland and Mansbach 1999). *P. viridis* contains the psychedelic compound N, N-dimethyltryptamine (DMT, Fig. 1), which acts as an agonist of serotonin (5-HT) receptors (Estrella-Parra et al. 2019). *B. caapi* contains the monoamine oxidase inhibitors harmine, harmaline, and tetrahydroharmine (Fig. 1), playing a crucial role in preventing the gastrointestinal degradation of DMT, which can then reach the central nervous system, where it exerts its psychoactive effects (Riba et al. 2012).

Several clinical studies have reported promising therapeutic effects of ayahuasca, including rapid and sustained reductions in depressive symptoms in patients with treatment-resistant major depressive disorder (Osório et al. 2015; Palhano-Fontes et al. 2015; Jiménez-Garrido et al. 2020). The mechanisms underlying the ayahuasca anxiolytic/antidepressant-like effects are not fully understood but have been attributed to its modulation of serotonergic, glutamatergic, and inflammatory pathways (Osório et al. 2015; Jiménez-Garrido et al. 2020; Santos et al. 2016; Soler et al. 2015). Based on behavioral data and psychometric self-report of 19 male experienced ayahuasca users, Sanches et al. (2024) suggested that the beverage can promote an emotion regulation mechanism in response to aversive stimuli with reduced anxiety and mental sedation. A recent study found that DMT administration led to a significant reduction in depressive symptoms just one day after treatment (Timmermann et al. 2024) and a phase-2 clinical trial conducted by Falchi-Carvalho et al. (2025) showed that inhaled DMT showed rapid and sustained

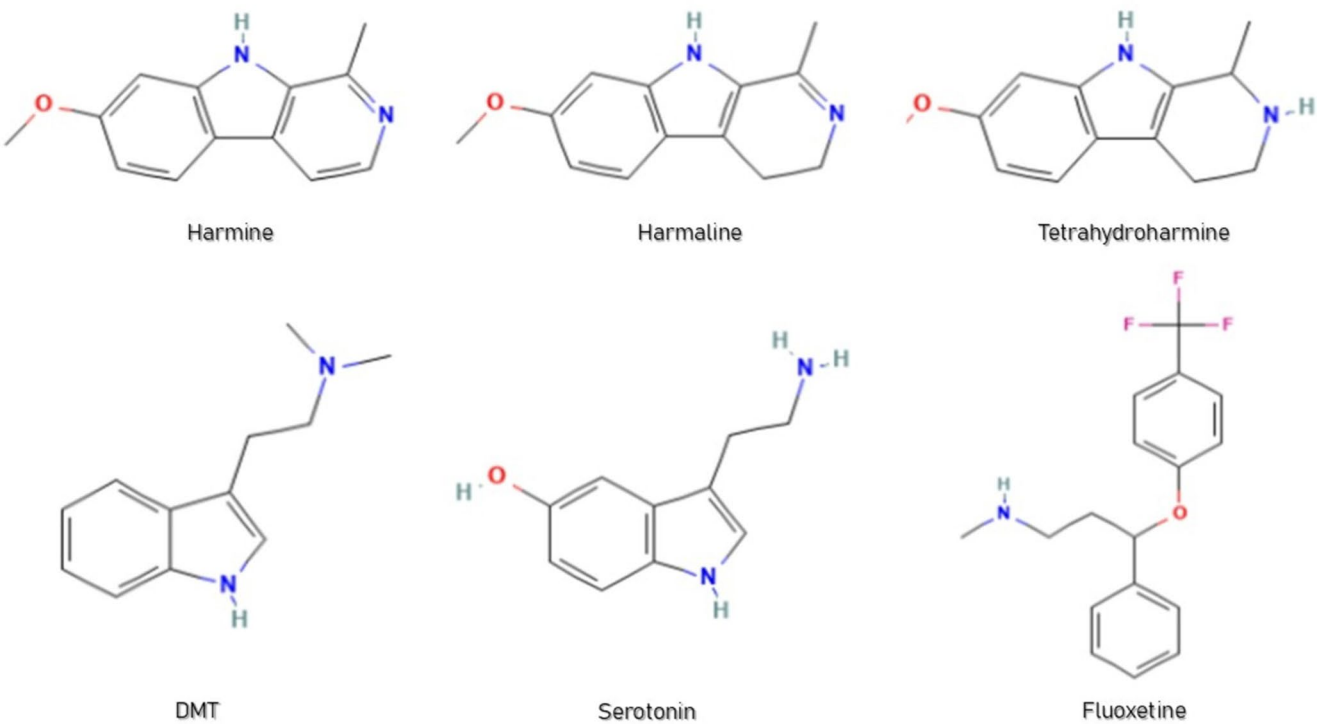

Fig. 1 Chemical structures of the main alkaloids present in ayahuasca (harmine, harmaline, tetrahydroharmine, and DMT), serotonin, and fluoxetine, a selective serotonin reuptake inhibitor antidepressant

antidepressant effects by day 7 ($p < 0.001$). Recent hypotheses suggest that DMT may have additional molecular roles, including the potential involvement of trace amine-associated receptor and sigma-1 receptor (Frecska et al. 2013), which may contribute to its significant anti-inflammatory effects (Riba et al. 2012; Rodrigues and Carlini 2006).

Peripheral cytokine profiles have been associated with brain function, well-being, and cognition (Bollen et al. 2017). The connection between inflammation and depression is further supported by evidence showing that elevated levels of interleukin (IL)−6 increase the risk of developing depression (Day and Giblin 2018; Rizzo et al. 2012). In the same way, high levels of IL-1β and Tumor Necrosis Factor (TNF) were associated with severe depression and suicidal ideation (Harsanyi et al. 2022; Liu et al. 2024). Additionally, studies have found microglial activation and neuroinflammation in the brains of patients with depression (Raison et al. 2006), which can be partially altered when therapy treatment is employed (Singh et al. 2024), highlighting the importance of therapeutic interventions that effectively modulate the brain's inflammatory response. Treatment of microglia BV-2 with *B. caapi* extract and some of its isolated components reduced proinflammatory cytokine production, suggesting their anti-inflammatory potential (Santos et al. 2022). Conversely, DMT has been shown to inhibit pro-inflammatory cytokines and chemokines while concurrently enhancing the expression of the anti-inflammatory cytokine IL-10 (Szabó et al. 2014).

Previous studies by our group and others evaluated the antidepressant potential of ayahuasca in Wistar rats after a single exposure, showing reduced exploratory behavior and locomotion in the open field test, and less immobility and more swimming behavior in the forced swimming test (Correa-Neto et al. 2017; Pic-Taylor et al. 2015; Colaço et al. 2020; Goulart da Silva et al. 2022), indicating an antidepressant effect. Moreover, the activation of c-Fos expression and Brain-derived Neurotrophic Factor (BDNF) in brain regions associated with serotonergic neurotransmission supports the role of ayahuasca components in interoception and emotional processing, which is modulated by serotonin pathways (Pic-Taylor et al. 2015; Colaço et al. 2020; Martinowich and Lu 2008).

This study aimed to evaluate the effects of ayahuasca and DMT on the modulation of the inflammatory profile of serum cytokines and on animal behavior in a rat model of lipopolysaccharide-induced depression.

Materials and methods

Ayahuasca, DMT and chemicals

The ayahuasca used in this study was prepared by the *União do Vegetal* church (UDV) in 2011 and has been used in previous research conducted by our group (Pic-Taylor et al. 2015; Noli et al. 2020; Colaço et al. 2020). Specimens of *B. caapi* vine and *P. viridis* leaves used to prepare the infusion were deposited in the University of Brasilia (UnB) Herbarium under the reference numbers Azevedo EP 149,880 BRAHMS and Trieto B 149,879 BRAHMS, respectively. The brew was stored at −20 °C until the study initiation. The ayahuasca brew was thawed, and a sample was reanalyzed by LC-MS/MS 6500 +QTRAP (AB Sciex, Framingham, USA), showing concentrations of 0.24 mg/mL of DMT, 1.53 mg/mL of harmine, 0.37 mg/mL of harmaline, and 0.42 mg/mL of tetrahydroharmine. DMT was synthesized, and its purity (above 98%) confirmed by LC-MS/MS 1 H and 13 C-NMR (Varian Mercury Plus Spectrometer 7.05 T operating at 300 MHz for 1 H and 75.46 MHz for 13 C), and LCMSD TOF (Agilent 1100 Series) using the DMT analytical standard (prod. SML0791; Sigma-Aldrich, USA).

Fluoxetine was obtained from *Farmacotecnica* (Brasilia, Brazil), lipopolysaccharide (LPS, E. coli strain OB111:B; prod. L3129), and phosphate-buffered saline (PBS) from Sigma-Aldrich Brazil LTDA (prod. P3813) and xylazine (prod. 2415) and ketamine (prod. 6544) from Vetnil (Brazil). Pro-inflammatory cytokines interleukin (IL)−1α (prod. 560159), IL-12p70 (prod. 558303), Tumor Necrosis Factor (TNF-α; prod. 558309), and interferon-γ (IFN-γ; prod. 558305), anti-inflammatory cytokines IL-4 (prod. 558307) and IL-10 (prod. 558306), and the CBA mouse/rat soluble protein master buffer kit (prod. 558266) were purchased from BD-Pharmigen (San Jose, CA, USA).

Animals and study design

The study was approved by the Animal Ethics Committee of the University of Brasilia (No. 23106.012384/2022-44).

A total of 126 male Wistar rats (Rattus norvegicus), aged 4 to 5 weeks and weighing an average of 190 g, were obtained from the Institute of Biology of the University of São Paulo, Brazil. The rats were acclimated for 10 days under controlled conditions in the animal facility of the Faculty of Medicine at the University of Brasília. The animals were housed in polypropylene cages with galvanized wire tops, in ventilated racks from Alesco®, maintained at a controlled temperature of 23 ±2 °C, relative humidity of 45 to 60%, and a 12-hour light/dark cycle. The animals were provided with commercial Purina® Rodent Chow and filtered water *ad libitum*. The animals' body weights were recorded every three days. The animals did not receive any form of environmental enrichment to avoid interfering with the stress-induced depression model.

The animals were induced into a "depression" state using LPS based on a protocol by Yang et al. (2018). The animals were divided into seven groups ($n = 18$ each). Gavage was

used in the animals from the saline control group, fluoxetine positive group (10 mg/kg body weight, bw), and three ayahuasca treatment groups corresponding (adjusted to the animal bw) to 0.5, 1 and 2x the usual dose of 150 mL taken by a 70 kg person used in a UDV ritual (Aya0.5, Aya1 and Aya2 groups). A 1x dose corresponds to 0.514 mg/kg bw of DMT, 3.28 mg/kg bw of harmine, 0.793 mg/kg bw of harmaline, and 0.900 mg/kg of tetrahydroharmine. These doses were the same as those used in the study by Colaço et al. (2020), which were selected based on previous studies showing that daily ayahuasca intake at doses 4x the usual dose or higher is fatal to male and female Wistar rats (Santos et al. 2017; da Motta et al. 2018).

Animals received LPS and DMT by intraperitoneal (ip) injection. LPS was administered to all animals, except the saline control, at 0.5 mg/kg bw, resuspended in PBS. The DMT dose (1 mg/kg DMT resuspended in PBS) corresponded approximately to the level of DMT received by the Aya2 group. The volume given to all animals at each dose (gavage or ip) was 2 mL.

On day 1 after acclimatization, the rats started receiving intraperitoneal LPS injections to induce depression-like behavior, which continued every other day until day 13. Starting on day 2, the animals received their respective doses of Aya, fluoxetine, or DMT daily until day 14. Figure 2 shows the experimental groups and a scheme of the protocol.

On the 15 th day, the animals underwent the open field and forced swimming tests and were anesthetized with a mixture of xylazine and ketamine (10 and 100 mg/kg bw, respectively). After confirming sedation and the absence of pain, nine animals per group were subjected to cardiac puncture for the collection of approximately 2 mL of blood, which was placed in a tube containing EDTA. The blood was centrifuged, and the plasma was stored at −80 °C for later analysis of inflammatory and anti-inflammatory cytokine levels. Following blood collection, the animals, still under strong sedative and analgesic effects, were immediately euthanized by guillotine, the brain removed and weighed.

Analysis of cytokines in serum

The assay was conducted according to the manufacturer's specifications (BD Cytometric bead array mouse/rat soluble protein master buffer kit). Samples were incubated for 1 h with antibody-coated beads and for an additional 2 h with detection antibody. After incubation, the plate was washed once, and the complex was suspended in the kit assay buffer. The BD LSRFortessa™ cytometer was used for data acquisition, and FCAP 3.0 software was employed for data analysis. A standard curve was generated for subsequent quantitative analysis, with results expressed in pg/mL.

Behavior tests

The 126 animals included in this study underwent behavioral tests 24 h after the last treatment to assess their behavior. The open field apparatus consisted of a circular white wooden arena, 96 cm in diameter and 34 cm in height, with the floor divided into 18 squares, with a central area. Each animal was placed in the central area, and its behavior was observed for 5 min and the following parameters were recorded: time in locomotion, number of crossing squares and entries into the central area, and frequency of rearing, grooming, defecation, and urination (Prut and Belzung 2003).

Following the open field, the forced swimming test was conducted in a transparent glass cylinder filled with water at 23 to 25 °C, to a depth of 30 cm, for 5 min. The time spent swimming, immobile, and climbing was recorded. Trained observers quantified the predominant behavior in each 5-second interval of the test (Slattery and Cryan 2012). All the behavior tests were video-monitored and analyzed further to confirm the observational data gathered during the tests. In both cases, the observers were blinded to group identification.

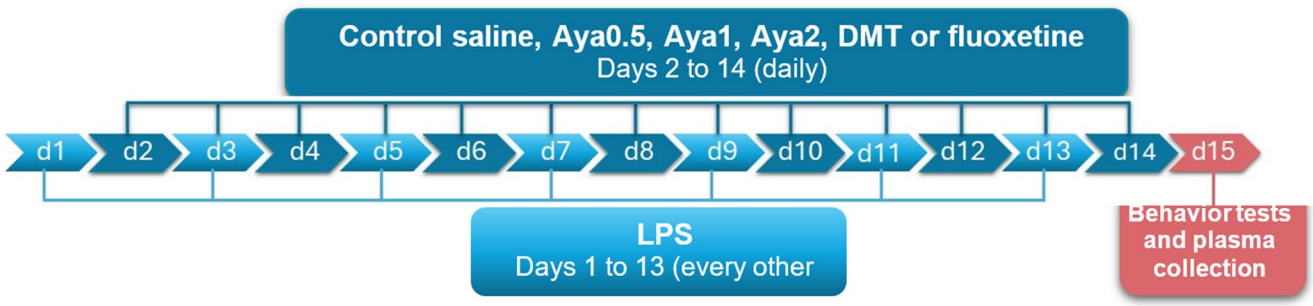

Fig. 2 Dose groups ($n = 18$ each) and experimental protocol used in the 15 days study period

Statistical analysis

The data were analyzed using GraphPad Prism 10.3.1 software. The data were first submitted to the Rout test to identify outliers (Q = 1%), and the clean data were verified for normality using Shapiro-Wilk and Kolmogorov-Smirnov tests. Data that passed the normality test ($p > 0.05$) was analyzed by one-way ANOVA followed by Tukey multiple comparisons. Data that did not pass the normality test ($p < 0.05$, nonparametric data) was analyzed with the Kruskal-Wallis test followed by Dunn´s. The values are expressed as mean ± standard error of the mean (SEM). Differences were considered statistically significant when $p \leq 0.05$.

Results

Body and brain weight

Figure 3 shows the body weight gain of the animals through the experiment (day 1 to day 15) and the brain weight relative to body weight (%). Body weight gain (Fig. 3a) was significantly higher in the control group compared to LPS ($p < 0.001$) and the treated groups ($p < 0.05$, $p < 0.001$ or $p < 0.0001$), except the Aya2 group. No differences were found between the LPS group and the treated groups. The DMT group had the lowest weight gain of all groups, which was significant compared to Aya1, Aya2 and fluoxetine groups ($p < 0.05$).

The Aya1 group showed a significantly lower brain weight related to body weight compared to all the other experimental groups, except for control, which was significantly lower than the Aya2 group (Fig. 3b). No significant correlation (Pearson or Spearman) was found between body weight gain and brain weight in all groups ($r = -0.02$ to -182; $p > 0.2$).

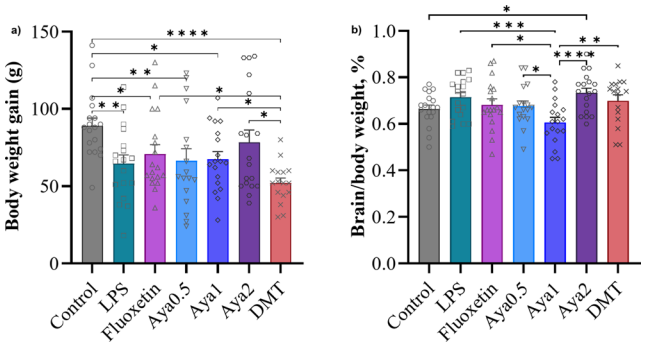

Fig. 3 (**a**) Body weight gain, (**b**) brain/body weight, %. Non-parametric analysis by Kruskal-Wallis, followed by Dunn's (body weight gain) or ordinary one-way ANOVA followed by Tukey. Each value represents the mean ± SEM of 14 to 18 animals per group. *$p < 0.05$, **$p < 0.01$, ***$p < 0.0005$ and ****$p < 0.0001$

Serum cytokine profile

Figure 4 shows the cytokine profile in the serum samples of each experimental group. The LPS treatment significantly increased the levels of the pro-inflammatory IL-1α cytokine compared to control ($p < 0.01$), indicating a robust induction of the pro-inflammatory response, which was significantly reversed in all treated groups (Fig. 4a).

The inflammatory TNF-α and IL-12p70 cytokine levels of the LPS group were higher than those of the control, although not statistically significant. However, these levels were significantly lower in all treated groups compared to the LPS group (Fig. 4b and c, $p < 0.05$ up to $p < 0.0005$). No significant differences were found in the IFN-γ levels among the groups (Fig. 4d).

Although not significant, LPS had higher anti-inflammatory IL-10 levels compared to control, which were significantly reverted in all treated groups (Fig. 4e, $p < 0.05$ to $p < 0.0001$). The fluoxetine group was the only one to exhibit an increase in IL-4 levels, with a significant difference from all other groups (Fig. 4f, $p < 0.05$).

Behavior tests

Overall, treatment with LPS had a limited impact on the animal behavior in both open field and swimming tests compared to control (Figs. 5 and 6). Total locomotion in the open field arena (number of quadrants crossed, including the central area) was significantly higher in the Aya2 group compared to the fluoxetine ($p < 0.05$) and DMT ($p < 0.01$) groups (Fig. 5a). Compared to control, the % of central entries relative to total locomotion was significantly higher ($p < 0.01$) in the Aya1 and Aya2 groups compared to control (Fig. 5b). Rearing behavior was higher in the Aya0.5 when compared to all other experimental groups, with higher significance for the fluoxetine group ($p < 0.0001$) (Fig. 5c). No significant differences were observed among the groups for urination and grooming (Fig. 5d and f) and defecation was higher in the LPS group, with significance ($p < 0.05$) only when compared to Aya0.5, Aya2 and DMT groups (Fig. 5e).

Figure 6 shows the results of the forced swimming test. Animals from the LPS group spent significantly ($p < 0.01$) less time swimming than the ayahuasca and DMT groups (Fig. 6a), and immobility was significantly ($p < 0.05$) higher compared to DMT (Fig. 6b). Furthermore, climbing behavior was lower in the LPS group, with significance ($p < 0.01$) when compared to fluoxetine and Aya0.5 groups, which showed a higher climbing activity compared to control (Fig. 6c). No significant differences in defecation were observed among the groups (Fig. 6d).

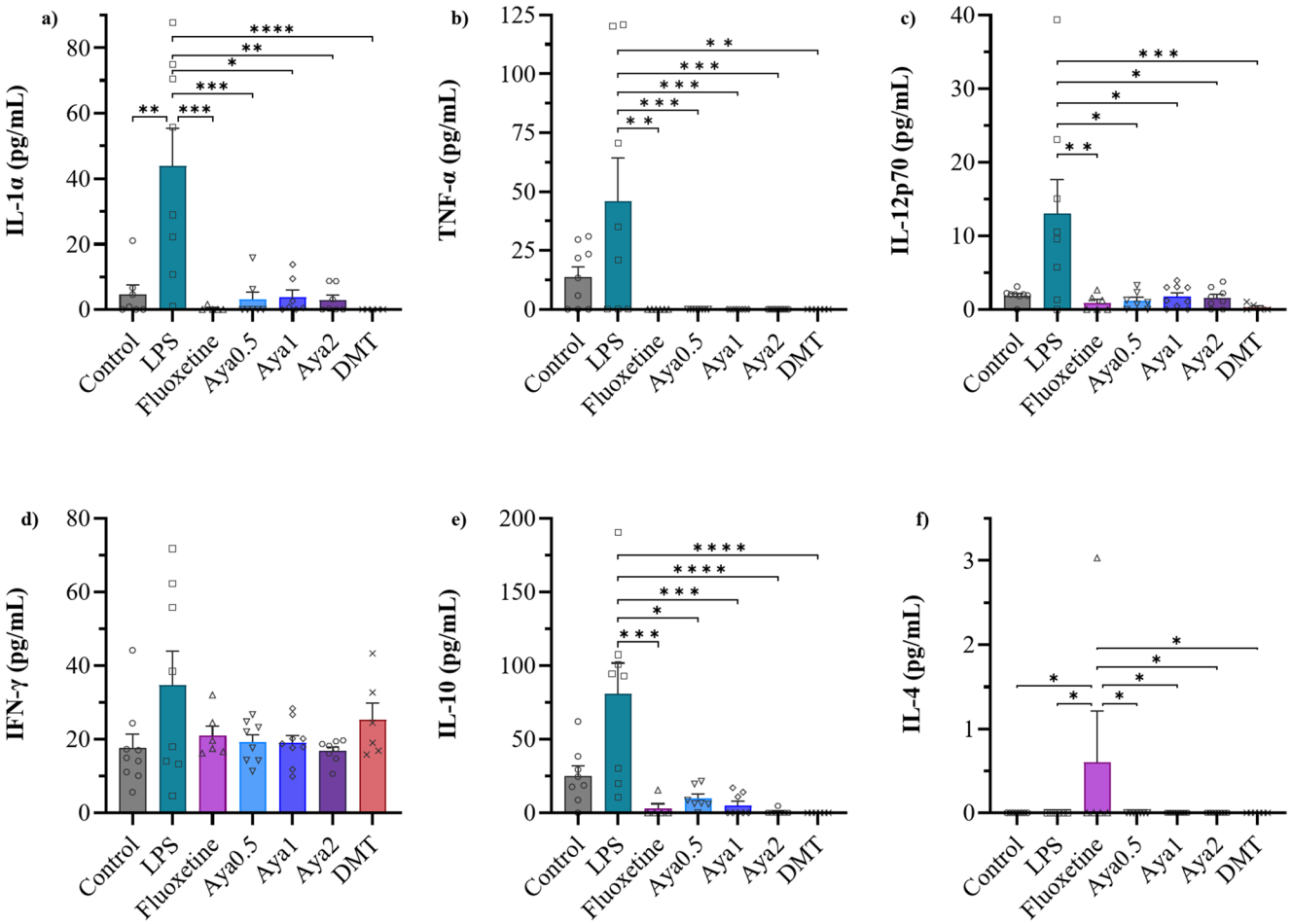

Fig. 4 Serum cytokine concentration of (**a**) IL-1α; (**b**) TNF-α; (**c**) IL-12p70; (**d**) IFN-γ; (**e**) IL-10; and (**f**) IL-4 (pg/mL). Non-parametric analysis by Kruskal-Wallis followed by Dunn's. Each value represents the mean ± SEM of 6 to 9 serum samples; *$p < 0.05$, **$p < 0.01$, ***$p < 0.0005$ and ****$p < 0.0001$

Discussion

The present study investigated the effects of ayahuasca, DMT, on the modulation of the serum cytokine profile and behaviors in a rat model of LPS-induced depressive behavior.

Decreased body weight gain and organ weight through an experiment may indicate a certain xenobiotic's toxicity (Bailey et al. 2004). In this study, the body weight gain has been negatively affected by most treatments compared to the control, which is expected for the LPS treatment as a consequence of an inflammatory process. However, treatment with fluoxetine, ayahuasca or DMT was not sufficient to revert this effect. LPS treatment did not impact brain weight (as % of bw), but the Aya1 group had significantly lower weight compared to all the other groups, a result not found previously by other studies conducted by our research group with the same ayahuasca material, and it is unlikely to have any biological relevance. In a 28 days chronic study conducted with ayahuasca (Aya0.5, Aya1 and Aya2), Colaço et al. (2020) only found a significant decrease in body weight gain in the fluoxetine group compared to the control, and no differences were found in the animal organs, including the brain. Similar to other studies (Bailey et al. 2004; Nirogi et al. 2014), no correlation was found between body and brain weight.

LPS can activate the immune system and induce microglia to produce pro-inflammatory cytokines, leading to behavioral and cognitive changes that resemble depressive symptoms (Dang et al. 2017; Yang et al. 2018). The LPS model used in this study was effective in inducing an inflammatory response, with increased plasma pro-inflammatory cytokines compared to the control, although significant only for IL-1α, an effect that was effectively reversed by fluoxetine, ayahuasca and DMT. On the other hand, although not significant, the levels of the anti-inflammatory IL-10 also increased in the LPS group compared to the control, a response that was also reversed by the treatments. LPS binds to TLR4 receptors located on the membranes of macrophages, the immune cells more frequent in the peritoneum. The downstream intracellular signaling triggered

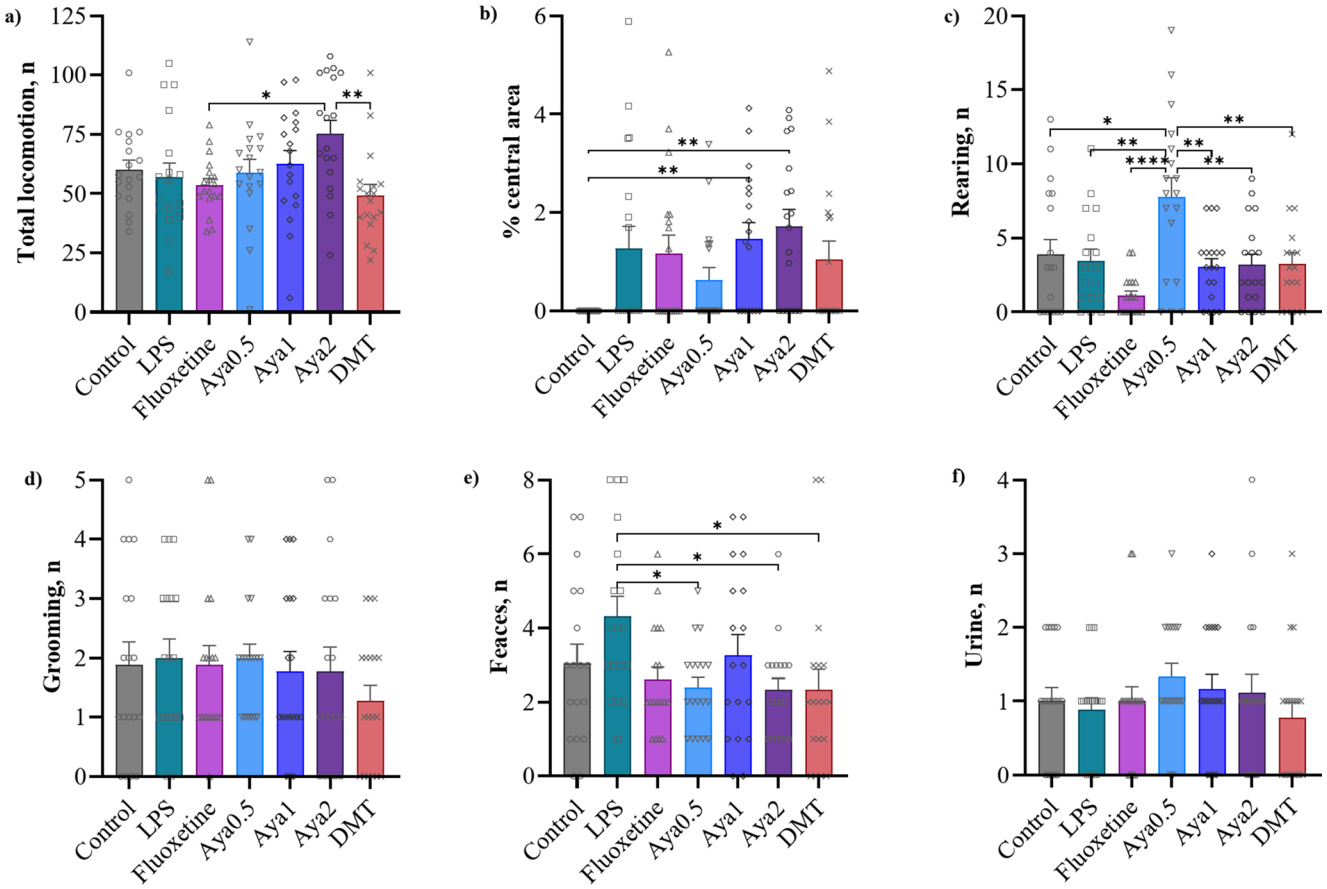

Fig. 5 Behavioral assessments in the open field test. (**a**) number of times crossing the open field quadrants; (**b**) % of entries into the central area compared to total locomotion; (**c**) rearing; (**d**) grooming; (**e**) defecation (number of fecal bolus), and (**f**) urination. Each value represents the mean ± SEM of 16 to 18 animals; *$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$

by this receptor initially promotes prolonged stimulation of inflammatory cytokines, such as TNF, via NFkB—independent of INF-γ activation. Over time, as the inflammatory response progresses, continuous LPS exposure can prompt the cell itself to counter-regulate LPS effects by producing IL-10 through ERK and p38 activation. Additionally, IL-10 may be secreted by TH1 and regulatory T cells as a negative feedback mechanism to prevent hypersensitivity reactions (Saraiva & O'Garra 2010; Yücel et al. 2017). The presence of IL-10 directly suppresses INF-γ production by TH1 cells (Kawai and Akira 2006; Antoniv and Ivashkiv 2011), which could explain the lower INF levels observed in certain LPS-challenged animals, although the mean levels were not significantly different from the control group. However, elevated INF levels can still coexist with IL-10 in immune responses. The balance between these two cytokines plays a crucial role in determining whether the antigen is effectively cleared or persists (Cope et al. 2011). Notably, four animals in the LPS study group exhibited high INF levels with concomitant IL-10 production. It is important to recognize that cytokine dynamics in antigen response and immune regulation/tolerance are highly complex within biological systems, particularly in organisms with different genetic backgrounds.

The findings of the present study support previous evidence (Voss Jr and Winkelhake 1974; House et al. 1990; Nkadimeng et al. 2021) regarding the potential of psychedelic substances to influence the immune system and reduce neuroinflammation associated with depression. A preliminary study indicated that lysergic acid diethylamide (LSD) may interfere with antibody production in rabbits by altering the antibody profile of activated B cells, leading to the production of low-molecular-weight proteins by influencing the translation process (Voss Jr and Winkelhake 1974). Another group demonstrated that in vitro exposure to high concentrations of LSD (100 µM) could significantly inhibit the proliferation and secretion of IL-2, IL-4, and IL-6 by B cells, as well as block the activation of CD8 + cytotoxic T cells (House et al. 1990). Psilocybin, a compound primarily produced by fungi of the genus *Psilocybe*, suppressed the inflammatory response induced by LPS stimulation in human U937 macrophages, probably through the inhibition of pro-inflammatory mediators such as COX-2 and pro-inflammatory cytokines (Nkadimeng et al. 2021).

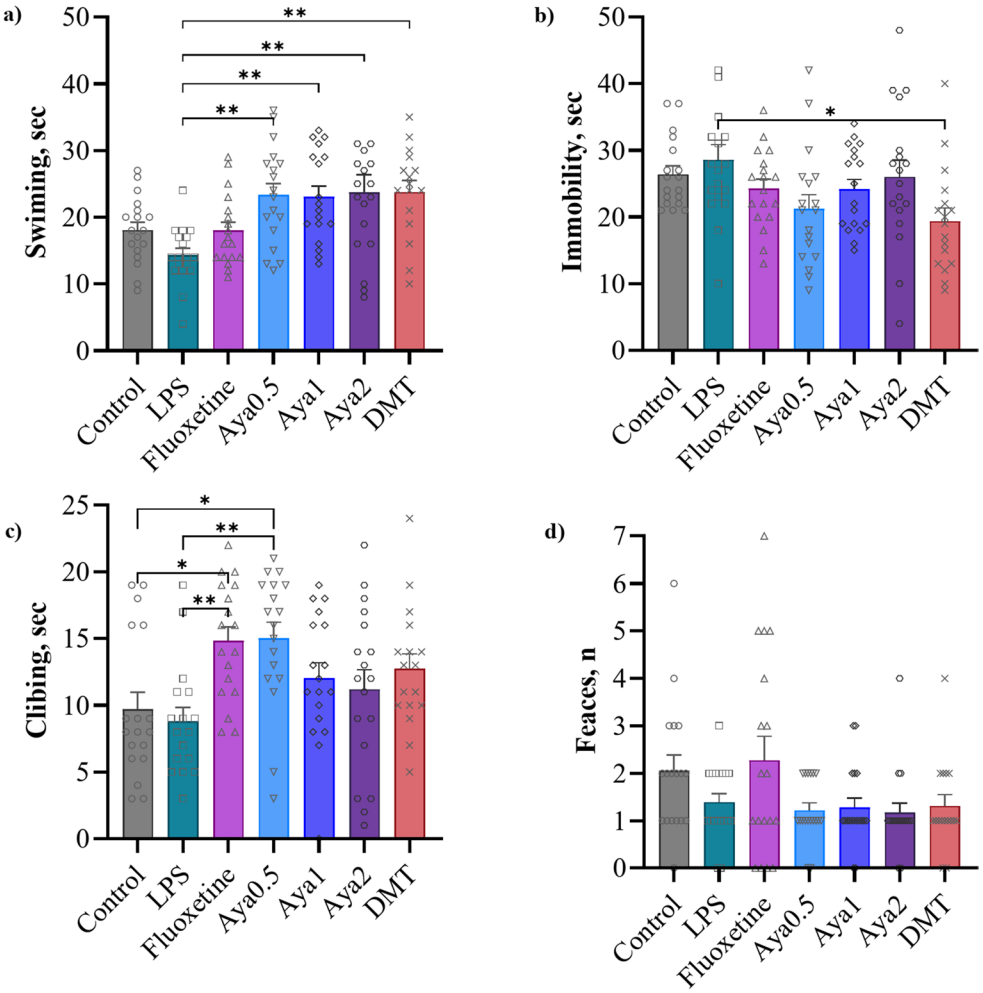

Fig. 6 Behavioral assessments in the forced swimming test. (**a**) Swimming time; (**b**) immobility time; (**c**) climbing time; (**d**) defecation. Each value represents the mean ± SEM of 16 to 18 animals; *$p < 0.05$ and **$p < 0.01$

DMT and its analog 5-MeO-DMT are known to reduce levels of IL-1β, IL-6, IL-8, and TNF-α while increasing IL-10 in human monocyte-derived dendritic cells under immunological challenge through sigma-1 receptors and serotonergic receptors (Szabó et al. 2014). This effect is comparable to the anti-inflammatory action observed in some SSRIs, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants (Köhler et al. 2016; Strawbridge et al. 2015), as well as in some anti-inflammatory therapies (Kappelmann et al. 2016). 5-MeOH also affects the glutamatergic system through NMDA (N-Methyl-D-Aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors (Dakic et al. 2017; Lima da Cruz et al. 2018; Ly et al. 2018), which are involved in synaptic plasticity and immune responses by inhibiting nuclear factor kappa B (NF-κB) pathways (Yu et al. 2008; Dakic et al. 2017). This complex interaction suggests that the immunomodulatory properties of psychedelics extend beyond simple cytokine regulation, offering potential new therapeutic avenues for inflammatory conditions related to psychiatric disorders.

The open field test was initially developed to measure emotionality in rodents, including locomotor activity and defecation (Hall 1934), and has been widely used as an animal model of anxiety-like behavior in drug testing (Prut and Belzung 2003; Seibenhener and Wooten 2015). In general, the test is based on the spontaneous exploratory behavior of rodents and their natural aversion to open areas caused by fear and anxiety, which is called thigmotaxis. The test has been validated with classical benzodiazepines, but the results with drugs that act as 5HT agonists or reuptake inhibitors (ip administration) are contradictory, showing decreased or increased locomotion behavior (Prut and Belzung 2003).

Yang et al. (2018) reported a significant decrease in body weight gain (which was also observed in the present study), locomotion and rearing in the open field in rats exposed to LPS (also at 0.5 mg/kg bw) every other day for 14 days compared to control, a clear indication of a depressive effect. In the present study, however, treatment with LPS did not significantly impact the rat behavior in the open field compared to the control, indicating that the test may

not have been sensitive enough to detect the depressive-like effect of LPS. This discrepancy may be because in the study by Yang et al. (2018), the test was conducted 24 h after the LPS dosing, while in the present study it was performed 48 h after dosing, which might have limited the detection of any behavior change. Notably, the Aya2 group exhibited the highest locomotion, significantly greater than the fluoxetine and DMT groups.

Rearing is considered an exploratory behavior and has been used as a measure of anxiety in the open field test; however, it is not clear whether rearing is anxiolytic or anxiogenic (Seibenhener and Wooten 2015). The observation that only the Aya0.5 group presented a significant increase in rearing behavior compared to the other treated groups may suggest a dose-dependent effect of ayahuasca on certain behavioral domains. Lower doses of Aya may have stimulatory effects on exploratory behavior, while higher doses could have different, perhaps even suppressive, effects. These different effects could be due to the complex mixture of compounds in ayahuasca and their varying interactions with the nervous system (Daldegan-Bueno et al. 2022).

In the open field test, increased time spent in the central part and/or a higher central/total locomotion ratio indicates anxiolysis (Prut and Belzung 2003), while defecation is negatively related to emotionality (Seibenhener and Wooten 2015). In the present study, all groups had a higher percentage of central area entries than the control, with the two highest ayahuasca doses showing significant increases. The ayahuasca and DMT groups exhibited significantly lower defecation behavior than the LPS group, results that confirm the anxiolytic effects in response to an inflammatory state.

Other studies with ayahuasca have reported contradictory results. Single oral doses of fluoxetine and ayahuasca (30 and 50x the usual dose) significantly decreased locomotion and rearing of male Wistar rats in the open field test one hour after dosing (Pic-Taylor et al. 2015). In a 28-day study, the percentage of central entries was significantly decreased after exposure to Aya1 and fluoxetine, but the authors highlighted that the test was applied one hour after the last exposure, which may reflect an acute effect (Colaço et al. 2020). Farias et al. (2022) reported a decrease in locomotion and time spent in the open field center 40 min after an oral dose of 500 mg/kg bw, which corresponds to 0.28 mg/kg DMT (~ Aya0.5 dose level). In a study with rats subjected to LPS-induced neuroinflammation, Goulart da Silva et al. (2022) reported anxiolytic behavior of rats treated with ayahuasca at a dose that corresponds to 1.4 mg/mL, as indicated by the higher time spent in the arena center.

The Forced Swimming Test (FST), first introduced by Porsolt et al. (1977), is a widely used model for assessing behavioral despair in rodents. When placed in a water-filled cylinder with no escape, the animals initially engage in vigorous behaviors such as swimming and climbing, in an attempt to escape. However, as the test progresses, they increasingly exhibit periods of immobility, a behavior interpreted not merely as reduced motor activity but as a manifestation of behavioral despair (Cryan and Holmes 2005). Thus, a reduction in immobility time generally indicates an antidepressant-like effect (Gutiérrez-García and Contreras 2009).

In the present study, treatment with LPS alone did not produce significant changes in any FST parameters compared to the control group, suggesting that the inflammatory challenge was insufficient to induce pronounced depressive-like behavior under the experimental conditions. However, administering ayahuasca and DMT led to significant behavioral modifications, with animals spending considerably more time swimming than the LPS group, implying an enhancement in active coping strategies and a reduction in behavioral despair. As noted by Cryan et al. (2002) and Detke et al. (1995), while antidepressant drugs typically decrease immobility, agents that boost noradrenergic transmission tend to increase climbing behavior; in contrast, those enhancing serotonergic transmission generally extend swimming time in the FST.

Pic-Taylor et al. (2015) reported that a single dose of ayahuasca increased swimming time in the FST. Similarly, Goulart da Silva et al. (2022) observed that rodents treated with ayahuasca to counteract LPS-induced neuroinflammation exhibited reduced immobility, underscoring the substance's antidepressant potential. MAO inhibitors in the brew may partially account for these effects. Fortunato et al. (2009) found that acute treatment with harmine (10 and 15 mg/kg) and imipramine (20 and 30 mg/kg) not only decreased immobility but also increased both swimming and climbing behaviors in rats—effects accompanied by reduced anhedonia, adrenal gland hypertrophy, and elevated BDNF levels in the hippocampus. In a related study, Lima et al. (2007) demonstrated that ayahuasca treatment reduced immobility time in a dose-dependent manner, with a lower reduction at higher doses. Moreover, the DMT-treated group exhibited a significant decrease in immobility time compared to the LPS group. Cameron et al. (2018) similarly found that administering DMT at 10 mg/kg significantly decreased immobility and increased rodent swimming time during the FST. Given that harmine alone has produced comparable outcomes in this test, it is plausible that both DMT and β-carboline alkaloids contribute to the antidepressant effects of ayahuasca. Additionally, DMT's ability to inhibit the serotonin transporter (Cozzi et al. 2009) may further underpin its antidepressant properties in the FST.

Furthermore, the fluoxetine and Aya0.5 groups increased climbing duration compared to the control and LPS groups. Chronic treatment with SSRIs has been shown to influence

neurotransmitter systems beyond serotonin; indeed, prolonged SSRI administration can enhance both serotonergic and noradrenergic functions (Page and Abercrombie 1997). This observation is consistent with the present results, as fluoxetine treatment increased climbing behavior, a response typically associated with acute antidepressant interventions that block norepinephrine reuptake. Therefore, the behaviors observed following chronic treatment likely reflect fluoxetine's combined impact on both serotonergic and noradrenergic systems.

In summary, the findings of this study are consistent with previous reports demonstrating the antidepressant-like effects of ayahuasca and its main psychoactive component DMT in various animal models of depression (Goulart da Silva et al. 2022; Palhano-Fontes et al. 2019; Cameron et al. 2018). The reduction in pro-inflammatory cytokines suggests that the antidepressant-like effects of ayahuasca and DMT may be mediated, at least in part, through the modulation of the inflammatory response.

Conclusions

The present study provides evidence that ayahuasca and DMT can modulate the inflammatory profile and produce antidepressant-like effects in an LPS-induced rat model of depression. These findings suggest a potential role for these compounds in the treatment of depression, a disorder strongly associated with chronic inflammation. However, further research is necessary to fully elucidate the underlying mechanisms and evaluate the clinical applicability of these promising therapeutic agents.

While the LPS model successfully induced an inflammatory response, as shown in the body weight gain and cytokine data, its effects on behaviors were limited. This suggests that the model might not fully capture all aspects of depression-like behavior, which can be considered a limitation of the study.

Future studies could explore the specific mechanisms underlying ayahuasca's and DMT's effects on different behaviors, investigate the role of other ayahuasca components, and consider alternative or complementary depression models. Further investigation into the apparent anxiolytic effect of DMT is also warranted.

Acknowledgements The authors thank the União do Vegetal Church for providing the ayahuasca beverage and acknowledge Bruno de Azevedo M. da Fonseca and Guilherme Antonio D. Carvalho for their assistance with laboratory animal care and procedures.

Author contributions DNS: original draft preparation, formal analysis, investigation. MA: formal analysis, investigation. MLS: formal analysis, investigation. TKSB: conceptualization, formal analysis, investigation, DMO: conceptualization, funding acquisition, reviewing and editing. EDC: conceptualization, funding acquisition, supervision, project administration, writing, reviewing and editing. All authors have read and agreed to the final version of the manuscript.

Funding This work received funding from the Brazilian National Council for Scientific and Technological Development (CNPq) Grant 408455/2021-7, the District Federal Research Foundation (FAP-DF) Grant 00193–0002410/2023-33 and the University of Brasilia (DPI 01/2022).

Data availability Data is provided within the manuscript.

Declarations

Ethical approval The study was conducted at the animal facility of the Faculty of Health Sciences, University of Brasilia, Brazil, in compliance with all federal requirements for animal care. The study was approved by the Animal Ethics Committee of the University of Brasilia (No.23106.012384/2022-44).

Competing interests The authors declare no competing interests.

References

Antoniv TT, Ivashkiv LB (2011) Interleukin-10-induced gene expression and suppressive function are selectively modulated by the PI3K-Akt-GSK3 pathway. Immunology 132(4):567–577. https://doi.org/10.1111/j.1365-2567.2010.03402.x

Bailey SA, Zidell RH, Perry RW (2004) Relationships between organ weight and body/brain weight in the rat: what is the best analytical endpoint? Toxicol Pathol 32(4):448–466. https://doi.org/10.1080/01926230490465874

Bollen JC, Trick L, Llewellyn DJ, Dickens C (2017) The effects of acute inflammation on cognitive functioning and emotional processing in humans: A systematic review of experimental studies. J Psychosom Res 93:1–12. https://doi.org/10.1016/j.jpsychores.2017.01.002

Bollini P, Pampallona S, Tibaldi G, Kupelnick B, Munizza C (1999) Effectiveness of antidepressants: meta-analysis of dose-effect relationships in randomised clinical trials. Br J Psychiatry 174:297–303. https://doi.org/10.1192/bjp.174.4.297

Cameron LP, Benson CJ, Dunlap LE, Olson DE (2018) Effects of N,N-Dimethyltryptamine on rat behaviors relevant to anxiety and depression. ACS Chem Neurosci 9(7):1582–1590. https://doi.org/10.1021/acschemneuro.8b00134

Colaço CS, Alves SS, Nolli LM, Pinheiro DJL, Rocha JA, Pic-Taylor A et al (2020) Toxicity of ayahuasca after 28 days daily exposure and effects on monoamines and brain-derived neurotrophic factor (BDNF) in brain of Wistar rats. Metab Brain Dis 35(4):739–751. https://doi.org/10.1007/s11011-020-00547-w

Cope A, Le Friec G, Cardone J, Claudia Kemper C (2011) The Th1 life cycle: molecular control of IFN-γ to IL-10 switching. Trends Immunol 32(6):278–286. https://doi.org/10.1016/j.it.2011.03.010

Correa-Netto NF, Masukawa MY, Galduróz JCF, Linardi A (2017) An ontogenic study of the behavioral effects of chronic intermittent exposure to Ayahuasca in mice. Braz J Med Biol Res 50(6):e6036. https://doi.org/10.1590/1414-431X20176036

Cozzi NV, Gopalakrishnan A, Anderson LL, Feih JT, Shulgin AT, Daley PF et al (2009) Dimethyltryptamine and other hallucinogenic tryptamines exhibit substrate behavior at the serotonin uptake transporter and the vesicle monoamine transporter. J Neural Transm 116(12):1591–1599. https://doi.org/10.1007/s00702-009-0308-8

Cryan JF, Holmes A (2005) The ascent of mouse: advances in modelling human depression and anxiety. Nat Rev Drug Discov 4(9):775–790. https://doi.org/10.1038/nrd1825

Cryan JF, Markou A, Lucki I (2002) Assessing antidepressant activity in rodents: recent developments and future needs. Trends Pharmacol Sci 23(5):238–245. https://doi.org/10.1016/S0165-6147(02)02017-5

Cuijpers P, Harrer M, Miguel C, Čihařová M, Karyotaki E (2023) Five decades of research on psychological treatments of depression: A historical and meta-analytic overview. Am Psychol 78(9):875–892. https://doi.org/10.1037/amp0001250

da Motta LG, de Morais JA, Tavares ACAM, Vianna LMS, MortariMR, Amorim RFB, Carvalho RR, Paumgartten FJR, Pic-Taylor A, Caldas ED (2018) Maternal and developmental toxicity of the hallucinogenic plant-based beverage ayahuascain rats. Reprod Toxicol 77:143–153. https://doi.org/10.1016/j.reprotox.2018.03.002

Dakic V, Minardi Nascimento J, Costa Sartore R, Maciel RM, de Araujo DB, Ribeiro S et al (2017) Short term changes in the proteome of human cerebral organoids induced by 5-MeO-DMT. Sci Rep 7(1):12863. https://doi.org/10.1038/s41598-017-12779-5

Daldegan-Bueno D, Favaro VM, Morais PR, Sussulini A, Oliveira MGM (2022) Effects of repeated Ayahuasca administration on behaviour and c-Fos expression in male rats exposed to the open field. Behav Brain Res 427:113878. https://doi.org/10.1016/j.bbr.2022.113878

Dang R, Xu P, Guo Y, Han W, Liao D, Jiang P (2017) Dl-3-n-Butylphthalide improves lipopolysaccharide-induced depressive-like behavior in rats: involvement of Nrf2 and NF-κB pathways. Psychopharmacology 235(9):2573–2585. https://doi.org/10.1007/s00213-018-4949-x

Day A, Giblin PAH (2018) Insights into macrophage heterogeneity and cytokine-induced neuroinflammation in major depressive disorder. Pharmaceuticals 11(3):64. https://doi.org/10.3390/ph11030064

Detke MJ, Rickels M, Lucki I (1995) Active behaviors in the rat forced swimming test differentially produced by serotonergic and noradrenergic antidepressants. Psychopharmacology 121(1):66–72. https://doi.org/10.1007/BF02245592

Estrella-Parra EA, Almanza-Pérez JC, Alarcón-Aguilar FJ (2019) Ayahuasca: uses, phytochemical and biological activities. Nat Prod Bioprospect 9(4):251. https://doi.org/10.1007/s13659-019-0210-5

Falchi-Carvalho M, Palhano-Fontes F, Wießner I, Barros H, Bolcont R, Laborde S, Ruschi B, Silva S, Montanini D, Barbosa C et al (2025) Rapid and sustained antidepressant effects of vaporized N,N-dimethyltryptamine: a phase 2a clinical trial in treatment-resistant depression. Neuropsychopharmacology 50(6):895–903. https://doi.org/10.1038/s41386-025-02091-6

Farias CP, Victoria PP, Xavier J, Sekine FG, Ribeiro ES, Cognato GP, Carvalho HCW (2022) Behavioral characterization of Ayahuasca treatment on Wistar rats in the open field test. Braz J Pharm Sci 58:e21110. https://doi.org/10.1590/s2175-97902022e21110

Fortunato JJ, Réus GZ, Kirsch TR, Stringari RB, Stertz L, Kapczinski F et al (2009) Acute Harmine administration induces antidepressive-like effects and increases BDNF levels in the rat hippocampus. Prog Neuropsychopharmacol Biol Psychiatry 33(8):1425–1430. https://doi.org/10.1016/j.pnpbp.2009.07.021

Frecska E, Szabo A, Winkelman MJ, Luna LE, McKenna DJ (2013) A possibly sigma-1 receptor mediated role of dimethyltryptamine in tissue protection, regeneration, and immunity. J Neural Transm (Vienna) 120(9):1295–1303. https://doi.org/10.1007/s00702-013-1024-y

Freedland CS, Mansbach RS (1999) Behavioral profile of constituents in ayahuasca, an Amazonian psychoactive plant mixture. Drug Alcohol Depend 54(3):183–194. https://doi.org/10.1016/s0376-8716(98)00154-9

Goulart da Silva M, Daros GC, Santos FP, Yonamine M, de Bitencourt RM (2022) Antidepressant and anxiolytic-like effects of Ayahuasca in rats subjected to LPS-induced neuroinflammation. Behav Brain Res 434:114007. https://doi.org/10.1016/j.bbr.2022.114007

Gutiérrez-García AG, Contreras CM (2009) Stressors can affect immobility time and response to Imipramine in the rat forced swim test. Pharmacol Biochem Behav 91(4):542–548. https://doi.org/10.1016/j.pbb.2008.09.008

Hall CS (1934) Emotional behavior in the rat: defecation and urination as measures of individual differences in emotionality. J Comp Psychol 18(3):385–403. https://doi.org/10.1037/h0071444

Harsanyi S, Kupcova I, Danisovic L, Klein M (2022) Selected biomarkers of depression: what arethe effects of cytokines and inflammation? Int J Mol Sci 24(1):578. https://doi.org/10.3390/ijms24010578

Herman PM, Anderson ML, Sherman KJ, Balderson BH, Turner JA, Cherkin DC (2017) Cost-effectiveness of Mindfulness-based stress reduction versus cognitive behavioral therapy or usual care among adults with chronic low back pain. Spine 42(20):1511–1520. https://doi.org/10.1097/BRS.0000000000002344

House RV, Lauer LD, Murray MJ, Thomas PT, Ehrlich JP, Burleson GR et al (1990) Examination of immune parameters and host resistance mechanisms in B6C3F1 mice following adult exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. J Toxicol Environ Health 31(3):203–215. https://doi.org/10.1080/15287399009531449

Jiménez-Garrido DF, Gómez-Sousa M, Ona G, Dos Santos RG, Hallak JEC, Alcázar-Córcoles MÁ et al (2020) Effects of Ayahuasca on mental health and quality of life in Naïve users: A longitudinal and cross-sectional study combination. Sci Rep 10(1):4075. https://doi.org/10.1038/s41598-020-61169-x

Kappelmann N, Lewis G, Dantzer R, Jones PB, Khandaker GM (2016) Antidepressant activity of anti-cytokine treatment: A systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. Mol Psychiatry 23(2):335–343. https://doi.org/10.1038/mp.2016.167

Kawai T, Akira S (2006) TLR signaling. Cell Death Differ 13(5):816–825. https://doi.org/10.1038/sj.cdd.4401850

Köhler CA, Freitas TH, Maes M, de Andrade NQ, Liu CS, Fernandes BS et al (2016) Peripheral cytokine and chemokine alterations in depression: A meta-analysis of 82 studies. Acta Psychiatr Scand 135(5):373–387. https://doi.org/10.1111/acps.12698

Labate BC, Feeney K (2012) Ayahuasca and the process of regulation in Brazil and internationally: implications and challenges. Int J Drug Policy 23(2):154–161. https://doi.org/10.1016/j.drugpo.2011.06.006

Lima LM, Ferreira SM, Ávila AAL, Caldas ED (2007) Les effets de l'ayahuasca Sur Le système nerveux central: étude comportementale. Phytothérapie 5(5):254–257. https://doi.org/10.1007/s10298-007-0266-y

Lima da Cruz RV, Moulin TC, Petiz LL, Leão RN (2018) A single dose of 5-MeO-DMT stimulates cell proliferation, neuronal survivability, morphological and functional changes in adult mice ventral dentate gyrus. Front Mol Neurosci 11:312. https://doi.org/10.3389/fnmol.2018.00312

Liu F, Yang Y, Fan XW, Zhang N, Wang S, Shi YJ et al (2024) Impacts of inflammatory cytokines on depression: A cohort study. BMC Psychiatry 24(1):195. https://doi.org/10.1186/s12888-024-05639-w

Luna LE (1984) The healing practices of a Peruvian Shaman. J Ethnopharmacol 11:123–133. https://doi.org/10.1016/0378-8741(84)90035-7

Ly C, Greb AC, Cameron LP, Wong JM, Barragan EV, Wilson PC et al (2018) Psychedelics promote structural and functional neural

plasticity. Cell Rep 23(11):3170–3182. https://doi.org/10.1016/j.celrep.2018.05.022
Martinowich K, Lu B (2008) Interaction between BDNF and serotonin: role in mood disorders. Neuropsychopharmacology 33(1):73–83. https://doi.org/10.1038/sj.npp.1301571
Nirogi R, Goyal VK, Jana S, Pandey SK, Gothi A (2014) What suits best for organ weight analysis: review of relationship between organ weight and body/brain weight for rodent toxicity studies. Int J Pharm Sci Res 5(4):1525–1532. https://doi.org/10.13040/IJPSR.0975-8232.5(4).1525-32
Nkadimeng SM, Steinmann CML, Eloff JN (2021) Anti-Inflammatory effects of four Psilocybin-Containing magic mushroom water extracts in vitro on 15-Lipoxygenase activity and on Lipopolysaccharide-Induced Cyclooxygenase-2 and inflammatory cytokines in human U937 macrophage cells. J Inflamm Res 14:3729–3738. https://doi.org/10.2147/JIR.S317182
Noli LM, Colaço CS, Alves SS, Pinheiro DJL, Rocha JA, Pic-Taylor A et al (2020) Effects of the hallucinogenic beverage Ayahuasca on voluntary ethanol intake by rats and on cFos expression in brain areas relevant to drug addiction. Alcohol 87:1–9. https://doi.org/10.1016/j.alcohol.2019.10.005
Osório FL, Sanches RF, Macedo LR, Santos RG, Maia-de-Oliveira JP, Wichert-Ana L et al (2015) Antidepressant effects of a single dose of Ayahuasca in patients with recurrent depression: A preliminary report. Braz J Psychiatry 37(1):13–20. https://doi.org/10.1590/1516-4446-2014-1496
Page ME, Abercrombie ED (1997) An analysis of the effects of acute and chronic Fluoxetine on extracellular norepinephrine in the rat hippocampus during stress. Neuropsychopharmacology 16(6):419–425. https://doi.org/10.1016/S0893-133X(96)00281-3
Palhano-Fontes F, Barreto D, Onias H, Andrade KC, Novaes MM, Pessoa JA et al (2015) The psychedelic state induced by Ayahuasca modulates the activity and connectivity of the default mode network. PLoS ONE 10(2):e0118143. https://doi.org/10.1371/journal.pone.0118143
Palhano-Fontes F, Barreto D, Onias H, Andrade KC, Novaes MM, Pessoa JA et al (2019) Rapid antidepressant effects of the psychedelic Ayahuasca in treatment-resistant depression: A randomized placebo-controlled trial. Psychol Med 49(4):655–663. https://doi.org/10.1017/S0033291718001356
Pic-Taylor A, da Motta LG, de Morais JA, Junior WM, Santos AD, Campos LA et al (2015) Behavioural and neurotoxic effects of ayahuasca infusion (Banisteriopsis caapi and Psychotria viridis) in female Wistar rat. Behav Processes 118:102–110. https://doi.org/10.1016/j.beproc.2015.05.004
Porsolt RD, Le Pichon M, Jalfre M (1977) Depression: A new animal model sensitive to antidepressant treatments. Nature 266(5604):730–732. https://doi.org/10.1038/266730a0
Prut L, Belzung C (2003) The open field as a paradigm to measure the effects of drugs on anxiety-like behaviors: A review. Eur J Pharmacol 463(1–3):3–33. https://doi.org/10.1016/S0014-2999(03)01272-X
Raison CL, Capuron L, Miller AH (2006) Cytokines Sing the blues: inflammation and the pathogenesis of depression. Trends Immunol 27(1):24–31. https://doi.org/10.1016/j.it.2005.11.006
Riba J, McIlhenny EH, Valle M, Bouso JC, Barker SA (2012) Metabolism and disposition of N,N-dimethyltryptamine and Harmala alkaloids after oral administration of Ayahuasca. Drug Test Anal 4(7–8):610–616. https://doi.org/10.1002/dta.1344
Rivier L, Lindgren J-E (1972) Ayahuasca, the South American hallucinogenic drink: an ethnobotanical and chemical investigation. Econ Bot 26(2):101–129. http://www.jstor.org/stable/4253328
Rizzo SJS, Harrigan T, Bender RH (2012) Evidence for sustained elevation of IL-6 in the CNS as a key contributor of depressive-like phenotypes. Transl Psychiatry 2(12):e199. https://doi.org/10.1038/tp.2012.120
Rodrigues E, Carlini EA (2006) Use of South American plants for the treatment of neuropsychiatric disorders. Rev Bras Psiquiatr 28(Suppl 2):S103–S108. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6734676/
Rossi A, Barraco A, Donda P (2004) Fluoxetine: A review on evidence-based medicine. Ann Gen Hosp Psychiatry 3(1):2. https://doi.org/10.1186/1475-2832-3-2
Sanches RF, Lima LR, Dos Santos RG, Crippa JA, Hallak JE (2024) Emotion regulation effects of Ayahuasca in experienced subjects during implicit aversive stimulation: an fMRI study. J Ethnopharmacol 320:117430. https://doi.org/10.1016/j.jep.2023.117430
Santos RG, Osório FL, Crippa JA, Hallak JE (2016) Antidepressive and anxiolytic effects of ayahuasca: A systematic literature review of animal and human studies. Braz J Psychiatry 38(1):65–72. https://doi.org/10.1590/1516-4446-2015-1701
Santos AFA,Vieira ALS, Aline Pic-Taylor A, Caldas ED (2017) Reproductive effects ofthepsychoactive beverage ayahuasca in male Wistar rats after chronic exposure. Brazilian J Pharmacology 27:353–360. https://doi.org/10.1016/j.bjp.2017.01.006
Santos BWL, Moreira DC, Borges TKS, Caldas ED (2022) Components of Banisteriopsis caapi, a plant used in the Preparation of the psychoactive ayahuasca, induce anti-inflammatory effects in microglial cells. Molecules 27(8):2500. https://doi.org/10.3390/molecules27082500
Saraiva M, O'Garra A (2010) The regulation of IL-10 production by immune cells. Nat Rev Immunol 10(3):170–81. https://doi.org/10.1038/nri2711
Seibenhener ML, Wooten MC (2015) Use of the Open Field Maze to measure locomotor and anxiety-like behavior in mice. J Vis Exp 96:e52434. https://doi.org/10.3791/52434
Singh SB, Tiwari A, Katta MR, Kafle R, Ayubcha C, Patel KH et al (2024) The utility of PET imaging in depression. Front Psychiatry 15:1322118. https://doi.org/10.3389/fpsyt.2024.1322118
Slattery DA, Cryan JF (2012) Using the rat forced swim test to assess antidepressant-like activity in rodents. Nat Protoc 7(6):1009–1014. https://doi.org/10.1038/nprot.2012.044
Soler J, Elices M, Franquesa A, Barker S, Friedlander P, Feilding A et al (2015) Exploring the therapeutic potential of ayahuasca: acute intake increases mindfulness-related capacities. Psychopharmacology 233(5):823–829. https://doi.org/10.1007/s00213-015-4162-0
Strawbridge R, Arnone D, Danese A, Papadopoulos A, Herane Vives A, Cleare AJ (2015) Inflammation and clinical response to treatment in depression: A meta-analysis. Eur Neuropsychopharmacol 25(10):1532–1543. https://doi.org/10.1016/j.euroneuro.2015.06.007
Szabó A, Kovács A, Frecska E, Rajnavölgyi É (2014) Psychedelic N,N-Dimethyltryptamine and 5-Methoxy-N,N-Dimethyltryptamine modulate innate and adaptive inflammatory responses through the sigma-1 receptor of human monocyte-derived dendritic cells. PLoS ONE 9(8):e106533. https://doi.org/10.1371/journal.pone.0106533
Timmermann C, Zeifman RJ, Erritzøe D, Nutt D, Carhart-Harris RL (2024) Effects of DMT on mental health outcomes in healthy volunteers. Sci Rep 14(1):53363. https://doi.org/10.1038/s41598-024-53363-y
Voss HF Jr, Winkelhake JL (1974) Immunologic properties of bacterial lipopolysaccharide (LPS): III. Role of LPS in the induction of primary and secondary immune responses in vitro. J Immunol 112(4):1515–1524
Yang M, Dang R, Xu P, Guo Y, Han W, Liao D et al (2018) Dl-3-n-Butylphthalide improves lipopolysaccharide-induced depressive-like behavior in rats: involvement of Nrf2 and NF-κB pathways. Psychopharmacology 235(9):2573–2585. https://doi.org/10.1007/s00213-018-4949-x

Yu B, Becnel J, Zerfaoui M, Rohatgi R, Boulares AH, Nichols CD (2008) Serotonin 5-hydroxytryptamine2A receptor activation suppresses tumor necrosis factor-α-induced inflammation with extraordinary potency. J Pharmacol Exp Ther 327(2):316–323. https://doi.org/10.1124/jpet.108.143461

Yücel G, Zhao Z, El-Battrawy I, Lan H, Lang S, Li X, Buljubasic F, Zimmermann WH et al (2017) Lipopolysaccharides induced inflammatory responses and electrophysiological dysfunctions in human-induced pluripotent stem cell derived cardiomyocytes. Sci Rep 7(1):2935. https://doi.org/10.1038/s41598-017-03147-4