Journal of Stress Physiology & Biochemistry, Vol. 21, No. 3 2025, pp. 175 - 183 ISSN 1997-0838

ORIGINAL ARTICLE

OPEN ACCESS

Effects of acute administration of Ayahuasca on the oxidative stress and neuronal apoptosis in rats

Alceu Afonso Jordao[1], Alex Roberto Melgar-Figueroa[2], Erikson Felipe Furtado[3]

[1] *Department of Health Sciences, Ribeirão Preto School of Medicine, University of São Paulo. Brazil*

[2] *Post-Graduation Program in Toxicology, Faculty of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo. Brazil*

[3] *Department of Neuroscience and Behavioral Sciences. Ribeirão Preto School of Medicine, University of São Paulo, Brazil*

*E-Mail: *alceu@fmrp.usp.br*

Received March 26, 2025

Introduction: The ayahuasca have legal authorization for religious use and scientific research. There are few published studies to determine their neurotoxic risk.

Objective: Evaluate the potential toxicity of ayahuasca in Wistar rats on the neuronal apoptosis and its relation to systemic effects flags of oxidative stress.

Method: Neurotoxicity was assessed by ayahuasca occurrence of neuronal apoptosis by fluorescence of Caspase-3 and by TUNEL assay. During 21 days, by gavage, twelve Wistar rats received 2 ml of 50% ayahuasca and the control group received 2 ml of water. Glutathione, malonaldehyde and vitamin E analyzes were performed to evaluate serum and hepatic lipid peroxidation as well as creatinine and urea analyzes for assessing kidney function.

Results: The caspase-3 showed no differences between the two groups. The values of serum MDA, serum glutathione and hepatic vitamin E showed a statistically significant reduction in the group treated with ayahuasca. Rats treated with ayahuasca also had higher mean value statistically significant apoptotic neurons, measured by TUNEL assay.

Conclusions: The results of this research indicate the presence of a process of oxidative stress in rats treated with ayahuasca, with statistically significant findings neuronal apoptosis assay with TUNEL. The reduced levels of serum MDA in ayahuasca group could point to a probable neuroprotective effect, however were also accompanied by a reduction in GSH and vitamin E, which indicates the occurrence of increased oxidative stress in this group.

Key words: Ayahuasca, Neurotoxicity, Neuronal Apoptosis, Oxidative Stress

Despite the tradition of its use in shamanic contexts, the use of ayahuasca (ayahuasca) has caused much controversy. In 1987, the substance was legalized officially, and in 2006, in Brazil CONAD authorized its religious use and for scientific research (CONAD, 2006).

There are few published studies that evaluate and determine the neurotoxic risk ayahuasca in experimental animals, specifically in apoptotic processes, and there is still much controversy between the neuroprotective and neurotoxic effects of its components.

Ayahuasca is a hallucinogenic drink, whose main components are harmine-HRM, harmaline-HRL, the tetrahydro-harmine-HHT and N, N-dimethyltryptamine-DMT (McKenna *et al.*, 1984a; McKenna *et al.*, 1984b; Freedland, Mansbach, 1999; Oliveira *et al.*, 2010).

DMT is a serotonin psychotropic agent that can cause changes in perception of reality with mental complex formation images (McKenna *et al.*, 1984a; McKenna *et al.*, 1984b; Callaway *et al.*, 1999; Carlini, 2003). Other neurophysiological effects of the beta-carbolines include competitive inhibition of dopamine, epinephrine, and norepinephrine in synaptosomes; in the synthesis of biogenic amines and possible role in benzodiazepines receptors (McKenna, 2004).

Several authors have described the neuroprotective properties of β-carbolines (Lee *et al.*, 2000; Kim *et al.*, 2001; Park *et al.*, 2003; Moura *et al.*, 2007) but also as neurotoxins have been proposed, particularly for damage to mitochondria (Uezono *et al.*, 2001; Chen et al, 2005; Song *et al.*, 2006).

The dimetiltriptamine has been considered neurotoxic and since 1971 is included in Level I of the Convention of the United Nations Psychotropic Substances (Pires et al,. 2010).

The aim of this study was to create an exploratory process that would allow evaluate the toxic potential of ayahuasca in Wistar rats as the parameters of oxidative stress, as well as its relationship to neuronal apoptosis.

MATERIALS AND METHODS

Obtaining composition and dosage of ayahuasca

The ayahuasca used in this work was obtained from the Laboratory of Toxicological (LAT), Faculty of Pharmaceutical Sciences USP in 2008. A team of researchers in the laboratory extracted alkaloids by using solid phase and gas chromatography with detector nitrogen- phosphorus (GC-NPD) reported the determination of its constituents, namely: DMT = 0.42mg / ml; HRM = 1.37 mg / ml; HRL = 0.62 mg / ml; HHT = 0.35 mg / 16 ml.

One study examined the effects of ayahuasca in rats concluded that administration of a dose of 500 mg / kg did not produce neurological impairment. The authors defined the LD_{50} in rats of ayahuasca at 5.83 g / kg. This same dosage and equivalent parameters determined were used in this study the administration of the ayahuasca experimental group (Souza-Brito *et al.*, 2010) (17).

Animals and experimental conditions

Twenty four Wistar male rats with initial weight of approximately 200 g, provided by the Central Animal Biotery of USP-RP were randomly divided into two groups of twelve animals each. They were placed in groups of four in plastic boxes with six metallic grid with food and water *ad libitum*. They were housed in the animal house of the Department of Internal Medicine of FMRP/USP, with a cycle of 12 hours light-dark, light off at 18:00 hours, and controlled constant temperature of 24-26ºC, passing through an adjustment period of two days .

Twelve rats were given by gavage a daily oral dose of 2 ml of 50% ayahuasca (ayahuasca group), while the control group received 2 ml of drinking water for twenty-one days. It was then a weekly routine weighing and urine collection in metabolic cages for 24 hours.

At the end of treatment, animals were euthanized by decapitation. They were extracted the brain, liver and whole blood from each animal for biochemical analysis in Laboratory of Nutrition and Metabolism of the Department of Internal Medicine of Ribeirão Preto-USP.

Coronal sections were performed on hippocampal region (approximately bregma-3.80 mm), and the obtained section was placed in 4% paraformaldehyde. inclusion histological procedures were performed on paraffin; Microtome at 5 um and stained with hematoxylin-eosin being assembled the blade with glass coverslips with sections through Entellan (Merck ®). The

remaining brain tissue was placed in the middle of homogenization to brain, ground and frozen at -18 ° C. The whole blood was removed and centrifuged at 3500 rpm for 10 minutes and the serum frozen for subsequent analysis obtained Glutathione (GSH), malonaldehyde (MDA) and vitamin E.

Losses Sampling

The sample size of the control group on Friday weighing decreased to ten subjects, due to the death of two mice in this group. At necropsy performed there has been no significant finding. The same situation happened to a mouse ayahuasca group on the day of sacrifice, which is why the number of this group appears as twelve in some analyzes and eleven others. In the evaluation of the tunnel, the sample number of both groups decreased to six due to the impossibility of remaining brain samples for neuronal apoptosis analysis.

Biochemical Methods

Quantification of total protein

By the Biuret method and using a colorimetric commercial kit (Labtest®).

Qquantification of reduced glutathione-GSH

GSH was quantified by colorimetric method, which consists in the reaction of this molecule with 5,5'-dithiobis-2-nitrobenzoic acid (DTNB), and subsequent reading in a spectrophotometer.

For quantification of serum GSH was added 1 mL of Tris-EDTA 25 ul of each serum sample in a test tube packed on ice; homogenized sample was performed and absorbance read at a wavelength of 412 nm, that subsequently were discounted from the second absorbance reading, in order to eliminate serum interference. Then the samples were poured into respective test tubes and 25 ul were added DTNB. After shake them, the absorbance read at 412 nm. The same procedure was performed with blank which did not have the serum sample. The concentration was calculated using a standard curve of GSH-EDTA (0.02M) with known concentrations of GSH each reading.

Quantification of Malondialdehyde

Was performed by determination of thiobarbituric acid reactive substances as follows: added one ml of 1.15% KCl 100 mg tissue; macerated and the mixture were added 2 ml solution of TBA-TCA-HCl (15% trichloroacetic acid, 0.375% thiobarbituric acid and 0.25 N hydrochloric acid); The mixture was heated for fifteen minutes in boiling water bath, cooled and centrifuged for ten minutes at 3000 rpm at room temperature and the supernatant used for reading at 535 nm in a spectrophotometer.

To 100 ul of serum was added 200 of TBA-TCA-HCl. This mixture was heated for fifteen minutes in boiling water bath, cooled and centrifuged at 1000 g for ten minutes at room temperature. Was obtained supernatant was used for determination of absorbance at 535 nm. White used consisted solely by solution TBA-TCA-HCl.

For the definition of MDA concentration was applied molar absorption coefficient of the product (E535 = $1{,}56x10^5M^{-1}$ cm^{-1}). A standard curve was performed using stock solutions of MDA. The concentrations found in the samples were within this curve shows good linearity with the standard.

Quantification of Vitamin E

It was performed in liver and serum samples by high-performance liquid chromatography (HPLC) (Shimadzu chromatograph equipped with a detector UV / Visible). The equipment was calibrated with α-tocopherol standard solutions (Sigma ®), and before each reading was injected into a standard α-tocopherol solution. The concentration of vitamin E in the samples was calculated using the ratio of the area of the analyte and the internal standard, after obtaining a calibration curve with known concentrations.

Quantitation of urinary creatinine

The kit Doles® modified Jaffe colorimetric system was used for creatinine quantification based on the principle that this reacts with picrate in alkaline medium, forming a reddish-yellow colored complex.

Quantitation of urinary urea

For the determination of urea in urine of the rats used the EC Urea Labetest enzymatic-colorimetric system. The principle of this method is to hydrolyze the urea by the urease to ammonium ions and CO2. The ammonium ions react in alkaline pH with salicylate and sodium hypochlorite under the catalytic action of sodium nitroprusside to form indophenol blue.

Method laboratory for apoptosis neuronal Caspase-3 Assay

The total protein content of brain homogenates was quantified by the biuret method. For the determination of the enzymatic activity Caspase-3 using the fluorometric assay kit (R & D Systems, Cat No. BF1100).

The results were expressed as fluorescence values for the kit does not supply the caspase-3 standard.

TUNEL assay

A frontal section of each brain tissue was fixed immediately in 4% paraformaldehyde for five days. one second cut was more localized in the hippocampal region. For each section, two slides were prepared. For the detection of neuronal cells with DNA damage, induced by the use of ayahuasca, we used the TUNEL assay (Kit Colorimetric TUNEL System (Promega®) detecting the fragmentation of DNA (Gavrieli *et al.*, 1992).

The fragmented DNA can be histochemically analyzed with light microscopy by staining brown present in the cytoplasm and nucleus of cells. Only the neuronal cell bodies were analyzed and the results expressed in number of apoptotic cells visualized by area. Ten microscopic fields at 40x magnification were observed and used for counting apoptotic neuronal bodies. For this analysis we used the AxioVision® software (version 4.7.2). To obtain the images of the fields analyzed we used a Zeiss machine with capture camera JVC TK-1270.

Statiscal Analysis

Descriptive statistics (mean, minimum and maximum standard deviation) for characterizing the sample according to group (ayahuasca and control) and variables body weight changes, organ weight, renal function tests, and lipid peroxidation neurotoxicity were evaluated.

For analysis of dependent variables (treatment with ayahuasca) and independent (neurotoxicity) we used the Chi-square test to evaluate the difference in proportions between both groups, as well as parameters indicative of oxidative stress. For evaluating the mean difference between ayahuasca and control groups we used the non-parametric Mann-Whitney test. For the analysis of correlation between variables was used the Spearman correlation test. The significance level was 5% for all tests ($p \leq 0.05$).

For statistical analysis we used the Statistical Package for Social Science (SPSS) version 15.0.

RESULTS

The group treated with ayahuasca showed lower values than the control group, expressed as mean of weight gain and percentage gain; The standard deviation of both variables was higher in ayahuasca group, but no differences were statistically significant (Table 1).

The three measurements of urinary urea in mg / dl were higher in ayahuasca group compared to the control group, and the value of the third measurement statistically significant (Table 2).

Hepatic MDA had higher values in control rats; They were observed higher GSH values in ayahuasca group and vitamin E is markedly diminished in animals of this group showing statistically significant (Table 3).

Serum levels of MDA, GSH and vitamin E are decreased in the group receiving the ayahuasca, with statistical significance for MDA and GSH. The serum vitamin E value were not statistically significant (Table 4).

The Caspase-3 values was lower in ayahuasca group, but no statistical significance. The TUNEL assay values are also lower in the control group and ayahuasca have statistically significant values for neuronal apoptosis (Table 5).

Table 1. Weight gain values and gain percentage of ayahuasca and control groups, expressed in grams.

	Ayahuasca group (n = 12)			Control Group (n = 10)				
	M	**DP**	**Min. - Max.**	**M**	**DP**	**Min. - Max.**	**U**	**P**
Weight gain	112.83	28.45	67.00 to 169.00	118.60	15.15	99.00 to 148.00	52.00	0.60
gain percentage	55.82	13,90	35.62 to 82.84	57.91	7.94	46.70 to 74.75	54.00	0.69

Values expressed as mean (m); Standard Deviation (SD) and minimum and maximum values min-max.); Coefficient U = Mann-Whitney; p = statistical significance.

Table 2. Urea levels in urine samples (n=3) of ayahuasca and control groups, expressed in mg / dL.

Weekly measurements of urinary urea	Ayahuasca group				Group control				
	n	M	DP	Min. - Max.	n	M	DP	Min. - Max.	P
1	12	93.33	32.38	35.00 to 140.00	12	74.01	29.35	30.62 to 131.25	0.18
2	12	82.14	22,40	35.00 to 131.25	12	69.27	48.14	26.25 to 201.25	0.09
3	12	88.59	32.75	35.00 to 131.25	10	43.75	26.41	8.75 to 96.25	<0.01

Amounts of sampling (n); Medium (M); Standard Deviation (SD) and minimum and maximum values (min-max.); p = statistical significance.

Table 3. Hepatic levels of MDA (nmol / g protein), GSH (mol / g protein) and vitamin E (nmol /g tissue) in control or Ayahuasca groups.

	Ayahuasca group (n = 11)				Control Group (n = 10)					
	M	md	DP	Min. - Max.	M	md	DP	Min. - Max.	U	P
MDA	37.84	34.47	7.40	30.13 to 52.60	43.36	45.48	6.75	31.20 to 50.37	32,00	0.10
GSH	5.60	5.66	0.64	4.84 to 6.80	5.34	5.51	0.67	4.00 to 6.13	45.00	0.48
Vit. E	41.91	41.31	10.16	18.70 to 55.36	80.88	78.34	21.71	48.96 to 118.58	4.00	<0.01

Values expressed as mean (m); Median (Md); Standard Deviation (SD) and minimum and maximum values (Min - Max..); Coefficient U = Mann-Whitney; p = statistical significance.

Table 4. Serum levels of MDA (nmol / g protein), GSH (mmol / g protein) and vitamin E (nmol / ml) in control or Ayahuasca groups.

	Ayahuasca group (n = 11)				Control Group (n = 10)					
	M	md	DP	Min. - Max.	M	md	DP	Min. - Max.	U	P
MDA	26.60	25.35	4.50	21.12 to 33.08	30.70	29.95	4.60	25.60 to 38.46	27.00	0.05
GSH	0.61	0.71	0.35	0.04 to 1.30	1.20	1.18	0.32	0.81 to 1.80	9.50	<0.01
Vit E	4.69	4.18	1.56	2.89 to 8.19	6.20	5.65	2.32	3.58 to 11.41	29,00	0.07

Values expressed as mean (m); Median (Md); Standard Deviation (SD) and minimum and maximum values (Min - Max..); Coefficient U = Mann-Whitney; p = statistical significance.

Table 5 Values of caspase-3 and TUNEL in control or Ayahuasca groups, expressed in number and level of fluorescence positive cells, respectively.

	Ayahuasca group				Group control				
	n	M	DP	Min. - Max.	n	M	DP	Min. - Max.	P
Caspase-3	11	25.51	6.89	16.39 to 37.94	10	27.33	6.14	17.69 to 39.64	0.40
TUNEL	6	1.33	0.52	1.00 to 2.00	6	3.00	2.00	1.00 to 6.00	0.05

Amounts of sampling (n); Medium (M); Standard Deviation (SD) and minimum and maximum values (Min. - Max.). p = statistical significance.

DISCUSSION

There are some limitations found in this study: the difficulty of finding publications of previous studies on the neurotoxic effects of ayahuasca in experimental animals; absence of a specific and recognized animal model for this type of research; using natural compound

instead of standard synthetic active ingredients; lack of behavioral studies of animals after the use of ayahuasca; compound management techniques, because there is still no accurate knowledge of the pharmacokinetics and pharmacodynamics of ayahuasca in Wistar rats.

The results obtained in this study, there was a difference in mean weight for treated mice lost more weight ayahuasca compared to the control group. A toxicity study with pregnat Wistar rats treated with ayahuasca reports significant loss values of maternal weight, which was interpreted as a sign of toxicity of this substance (Oliveira *et al.*, 2010).

Another study related weight loss and malnutrition, depletion of GSH and oxidative stress (Wu *et al.*, 2004). As for the kidney function parameters, a urinary urea measurement showed higher values with statistical significance in the group of rats treated with ayahuasca, aren´t other studies with animal models treated with ayahuasca that validate these biochemical parameters. It is considered that the changes in the values of urea and creatinine urinary may represent a sign of renal damage in rats treated with ayahuasca. The analysis of kidney function are fundamentally important parameters in toxicity studies in animals and humans, since dehydration states, or stress the animals could, at some point, provide or initiate an apoptotic process.

Regarding the indicators of oxidative stress, comparative analyzes of serum levels of GSH and MDA well as hepatic vitamin E showed a statistically significant decrease in mice treated with ayahuasca.

Recent studies underscore the importance of an enabling intracellular environment to the changes in regulation of apoptosis in the redox environment and consider the depletion of GSH a common feature of cell death apoptosis triggered by a wide variety of stimuli including: activation of death receptors, stress agents environmental and cytotoxic drugs. This depletion of GSH, considered initially only as a byproduct of oxidative stress generated during cell death, is now seen as a critical regulator of apoptosis. Thus, a statistically significant reduction of serum levels of GSH in the group of rats treated with ayahuasca may indicate that oxidative stress may be contributing to a direct regulation of neuronal apoptosis. The apoptotic process is regulated by cascades intrinsic and extrinsic signaling. It is demonstrated that depletion of GSH can activate both apoptotic signaling pathways in several control points, predisposing cells to apoptosis or directly triggering the death cellular (Franco, Cidlowsky, 2009). Also the MDA elevated in various diseases and intoxication, it has been linked to damage caused by free radicals, produced by lipid peroxidation processes (Mateos *et al.*, 2005; Antunes *et al.*, 2008).

Unlike the results reported in the literature in this study were found reduced serum and hepatic MDA levels in the group of rats treated with ayahuasca, which could be an indication of a proper antioxidant action mechanism of the substance probably the content of ß-carbolines because this molecule have been described as neuroprotective.

With respect to vitamin E, they were found significantly decreased levels and statistical significance analysis in liver of rats treated with ayahuasca. Vitamin E is an important antioxidant that is consumed in an attempt to avoid cellular imbalance oxidative stress (Jordão *et al.*, 1998) and decreased values could suggest the presence of oxidative stress induced by ayahuasca consumption. At the moment there are no other published studies on the occurrence of this phenomenon (Jordão *et al.*, 1998).

The TUNEL assay carried out for evaluation of the occurrence of neuronal apoptosis, the group of rats treated with ayahuasca had higher mean value statistically significant apoptotic neurons. In a study relating apoptosis and oxidative stress, or authors suggest that oxidative stress may interfere with the activation of caspases and throughout the apoptotic process by depletion of adenosine triphosphate (ATP) intracellular and may even derive it to necrosis (Lee, Shacter, 1999).

Based on the results of biochemical analyzes of mice treated with ayahuasca in the present study, we consider the possibility of an oxidative stress process, and perhaps for this reason neuronal apoptosis is increased in this group of animals.

Another way to neurotoxicity produced by use of

ayahuasca could be the existence of cell microinjuries caused by cerebral ischemia / reperfusion. These lesions could initiate a complex series of biochemical and molecular events with loss of function by disruption of the cell integrity due to glutamatergic excitotoxicity, the ionic imbalance, the reactions of free radicals and poly polymerase activation- PARP (Zhang *et al.*, 2009). This is the protein that binds to DNA protects its integrity and facilitating the repair of ruptures in their chains and is involved in important biological processes such as: genome integrity monitoring, response initiation DNA damage and apoptosis (Isabelle *et al.*, 2010).

However others authors showed the therapeutic properties of ayahuasca components in ischemia/reperfusion injury of the eye (Szilágyi *et al.*, 2022).

Ayuhasca treatment counteracted biochemical alterations, as MDA and nitrite levels in a model of depression elicited by unpredictable chronic mild stress but did not display any alterations in non-stressed rats (Xavier *et al.*, 2021).

In one recent study ayahuasca showed as a promising approach to prevent sepsis-induced neuroinflammatory and oxidative stress, with reduced values of thiobarbituric acid reactive substances (de Camargo *et al.*, 2025).

The ayahuasca intake may have interfered with the apoptotic process in rats for several reasons: change in cell structure due to ischemia; cytotoxicity of oxidative stress secondary to depletion of GSH and vitamin E; glutamatergic or possible biochemical mechanisms.

Based on the results obtained, it can be said that there is a neurotoxic related to the use of ayahuasca process in the group of rats submitted to subacute treatment with this substance. The lower values of serum GSH and vitamin E hepatic found in this group of animals, as well as decreased body weight and increased urinary urea, compared to the control group values can be evidence of systemic signaling effects of stress oxidative and as a result, is indirectly impacting the actuation or the stimulation of a brain apoptotic process.

CONCLUSION

The unique findings of the present study that could hypothetically be indicative of neuroprotection induced by the use of ayahuasca are the values decreased MDA serum and liver, but not statistically significant, and at this time it is not possible to categorically state that the ayahuasca has neuroprotective properties because as already highlighted with lower values were also accompanied by a reduction in GSH antioxidants and vitamin E, which indicates the occurrence of increased oxidative stress in this group or at least greater depletion of antioxidants, is necessary future studies in order to increase knowledge related to possible therapeutic or deleterious effects of ayahuasca.

CONFLICTS OF INTEREST

The authors declare that they have no potential conflicts of interest.

REFERENCES

Antunes, M. V., Lazzaretti, C., Gamaro, G. D., & Linden, R. (2008). Estudo pré-analítico e de validação para determinação de malondialdeído em plasma humano por cromatografia líquida de alta eficiência, após derivatização com 2, 4-dinitrofenilhidrazina. *Revista Brasileira de Ciências Farmacêuticas*, 44, 279-287.

Callaway, J. C., McKenna, D. J., Grob, C. S., Brito, G. S., Raymon, L. P., Poland, R. E., ... & Mash, D. C. (1999). Pharmacokinetics of Hoasca alkaloids in healthy humans. *Journal of ethnopharmacology*, 65(3), 243-256.

Carlini, E. D. A. (2003). Plants and the central nervous system. *Pharmacology Biochemistry and Behavior*, 75(3), 501-512.

Chen, Q., Chao, R., Chen, H., Hou, X., Yan, H., Zhou, S., ... & Xu, A. (2005). Antitumor and neurotoxic effects of novel harmine derivatives and structure-activity relationship analysis. *International Journal of Cancer*, 114(5), 675-682.

CONAD 2006: Conselho Nacional Antidrogas. Grupo Multidisciplinar de Trabalho - GMT - Ayahuasca: Relatório Final. Disponível em: <http://www.ayahuascabrasil.org/index.php?

op=noticia010>. Acesso em: 19 jun. 2011.

de Camargo, R. W., Joaquim, L., Machado, R. S., de Souza Ramos, S., da Rosa, L. R., de Novais Junior, L. R., ... & de Bitencourt, R. M. (2025). Ayahuasca Pretreatment Prevents Sepsis-Induced Anxiety-Like Behavior, Neuroinflammation, and Oxidative Stress, and Increases Brain-Derived Neurotrophic Factor. *Molecular Neurobiology*, 62, 5695–5719.

Franco, R., & Cidlowski, J. A. (2009). Apoptosis and glutathione: beyond an antioxidant. *Cell Death & Differentiation*, 16(10), 1303-1314.

Freedland, C. S., & Mansbach, R. S. (1999). Behavioral profile of constituents in ayahuasca, an Amazonian psychoactive plant mixture. *Drug and alcohol dependence*, 54(3), 183-194.

Gavrieli, Y., Sherman, Y., & Ben-Sasson, S. A. (1992). Identification of programmed cell death in situ via specific labeling of nuclear DNA fragmentation. *Journal of cell Biology*, 119(3), 493-501.

Isabelle, M., Moreel, X., Gagné, J. P., Rouleau, M., Ethier, C., Gagné, P., ... & Poirier, G. G. (2010). Investigation of PARP-1, PARP-2, and PARG interactomes by affinity-purification mass spectrometry. *Proteome science*, 8, 1-11.

Jordão Júnior, A. A., Chiarello, P. G., Bernardes, M. S. M., & Vannucchi, H. (1998). Peroxidação lipídica e etanol: papel da glutationa reduzida e da vitamina E. *Medicina (Ribeirão Preto)*, 31(3), 434-449.

Kim, D. H., Jang, Y. Y., Han, E. S., & Lee, C. S. (2001). Protective effect of harmaline and harmalol against dopamine-and 6-hydroxydopamine-induced oxidative damage of brain mitochondria and synaptosomes, and viability loss of PC12 cells. *European Journal of Neuroscience*, 13(10), 1861-1872.

Lee, C. S., Han, E. S., Jang, Y. Y., Han, J. H., Ha, H. W., & Kim, D. E. (2000). Protective effect of harmalol and harmaline on MPTP neurotoxicity in the mouse and dopamine-induced damage of brain mitochondria and PC12 cells. *Journal of neurochemistry*, 75(2), 521-531.

Lee, Y. J., & Shacter, E. (1999). Oxidative stress inhibits apoptosis in human lymphoma cells. *Journal of Biological Chemistry*, 274(28), 19792-19798.

Mateos, R., Lecumberri, E., Ramos, S., Goya, L., & Bravo, L. (2005). Determination of malondialdehyde (MDA) by high-performance liquid chromatography in serum and liver as a biomarker for oxidative stress: Application to a rat model for hypercholesterolemia and evaluation of the effect of diets rich in phenolic antioxidants from fruits. *Journal of Chromatography B*, 827(1), 76-82.

McKenna, D. J. (2004). Clinical investigations of the therapeutic potential of ayahuasca: rationale and regulatory challenges. *Pharmacology & therapeutics*, 102(2), 111-129.

McKenna, D. J., Towers, G. N., & Abbott, F. (1984a). Monoamine oxidase inhibitors in South American hallucinogenic plants: tryptamine and β-carboline constituents of ayahuasca. *Journal of ethnopharmacology*, 10(2), 195-223.

McKenna, D. J., Towers, G. N., & Abbott, F. S. (1984b). Monoamine oxidase inhibitors in South American hallucinogenic plants Part 2: Constituents of orally-active Myristicaceous hallucinogens. *Journal of Ethnopharmacology*, 12(2), 179-211.

Moura, D. J., Richter, M. F., Boeira, J. M., Pêgas Henriques, J. A., & Saffi, J. (2007). Antioxidant properties of β-carboline alkaloids are related to their antimutagenic and antigenotoxic activities. *Mutagenesis*, 22(4), 293-302.

Oliveira, C. D. R., Moreira, C. Q., de Sá, L. R. M., de Souza Spinosa, H., & Yonamine, M. (2010). Maternal and developmental toxicity of ayahuasca in Wistar rats. *Birth Defects Research Part B: Developmental and Reproductive Toxicology*, 89(3), 207-212.

Park, T. H., Kwon, O. S., Park, S. Y., Han, E. S., & Lee, C. S. (2003). N-methylated β-carbolines protect PC12 cells from cytotoxic effect of MPP+ by attenuation of mitochondrial membrane permeability change. *Neuroscience research*, 46(3), 349-358.

Pires, A. P. S., Oliveira, C. D. R. D., & Yonamine, M.

(2010). Ayahuasca: uma revisão dos aspectos farmacológicos e toxicológicos. *Revista de Ciências Farmacêuticas Básica e Aplicada*, 31(1), 15-23

Song, Z. Y., Liu, J. R., Lu, X. L., & Wang, L. J. (2006). Harmine induces apoptosis in human SGC-7901 cells. *Zhong yao cai= Zhongyaocai= Journal of Chinese Medicinal Materials*, 29(6), 571-573.

Souza-Brito, ARM, Antonio MA, Costa M, Carvalho JE, Dias PC. (1994), Efeitos farmacológicos do decocto (hoasca) de Banisteriopsis caapi e Psychotria viridis em camundongos.. In: *IX Reunião Anual da Federação das Sociedades de Biologia Experimental (FESBE), Caxambu, MG*. Resumos da IX Reunião Anual da FESBE. São Paulo: Editora da FESBE, p. 203.

Szilágyi, A., Takács, B., Szekeres, R., Tarjányi, V., Bombicz, M., Priksz, D., ... & Varga, B. (2022). Therapeutic properties of ayahuasca components in ischemia/reperfusion injury of the eye. *Biomedicines*, 10(5), 997.

Uezono, T., Maruyama, W., Matsubara, K., Naoi, M., Shimizu, K., Saito, O., ... & Shiono, H. (2001). Norharman, an indoleamine-derived β-carboline, but not Trp-P-2, a γ-carboline, induces apoptotic cell death in human neuroblastoma SH-SY5Y cells. *Journal of neural transmission*, 108, 943-953.

Wu, G., Lupton, J. R., Turner, N. D., Fang, Y. Z., & Yang, S. (2004). Glutathione metabolism and its implications for health. The Journal of nutrition, 134(3), 489-492.

Xavier, J., Farias, C. P., Soares, M. S. P., Silveira, G. D. O., Spanevello, R. M., Yonamine, M., ... & Cognato, G. D. P. (2021). Ayahuasca prevents oxidative stress in a rat model of depression elicited by unpredictable chronic mild stress. *Archives of Clinical Psychiatry (São Paulo)*, 48(2), 90-98.

Zhang, H. F., Hu, X. M., Wang, L. X., Xu, S. Q., & Zeng, F. D. (2009). Protective effects of scutellarin against cerebral ischemia in rats: evidence for inhibition of the apoptosis-inducing factor pathway. *Planta medica*, 75(02), 121-126.