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Research Article
Psychoactive and Organic Effects of *Banisteriopsis caapi* and *Diplopteris cabrerana* (Cuatrec.) B. Gates in Rats

[1]Américo Castro, [1]Norma Ramos, [2]Juan Rojas-Armas, [1]Sixto González, [1]Otilia Acha, [3]José Raez, [1]Donald Ramos and [4]Julio Hilario-Vargas

[1]Research Institute of Pharmaceutical Sciences and Natural Resources, School of Pharmacy and Biochemistry, National University of San Marcos, Lima-Peru
[2]Research Clinical Institute, Faculty of Medicine, National University of San Marcos, Lima-Peru
[3]Institute of Pathology, Faculty of Medicine, National University of San Marcos, Lima-Peru
[4]Department of Physiology, School of Medicine, National University of Trujillo, Trujillo-Peru

Abstract

Background and Objective: The Amazonian drink ayahuasca used traditionally for ritual, religious and healing purposes; currently is being increasingly used for recreational purposes in the USA and Europe. This study was carried out to evaluate the psychoactive and organic effects in rats by ingestion of *Banisteriopsis caapi* "Ayahuasca" and *Diplopteris cabrerana* (Cuatrec.) B. Gates. "Chaliponga." **Materials and Methods:** Extracts of both species were given orogastrically to adult albino rats, *Rattus novergicus* Holtzman strain. Seven groups of rats (n = 5) with an average weight of 240±30 g were given: (GI) control, (GII) 2.5 mL diazepam, (GIII) 0.7 mL solution of *Banisteriopsis caapi*, (GIV) 0.7 mL solution of *Diplopteris cabrerana* and in groups (GV), (GVI) and (GVII) was administered 0.7, 3.5 and 7.0 mL of the mixture of both extracts, respectively. Macroscopic and microscopic evaluations were also performed. The data were analyzed using the Chi-square test and Fisher's exact test. The statistical package used was (SPSS) version 20. **Results:** Phytochemical screening showed presence of alkaloids, anthraquinones, triterpenoids and steroids, phenols, flavonoids and saponins. In macroscopic evaluations it was observed that reflexes and motor activity were reduced. The mixture of both extracts produced dose-dependent effects. The GVII showed passivity, reduced motor activity, motor loss of lower limbs, strong convulsions, facial tremors, diuresis, irritability and spasms. In microscopic analysis there were observed alterations in the brain, cerebellum, liver and aorta. These changes arose from the first doses and increased with doses of 3.5 and 7.0 mL. **Conclusion:** The present study revealed that the ingestion of *Banisteriopsis caapi*+*Diplopteris cabrerana* mixture has psychoactive and organic effects in rats at the doses administered so the study must be taken into account for future experimentation.

Key words: *Banisteriopsis caapi*, *Diplopteris cabrerana*, ayahuasca, psychoactive, convulsions, tremors, spasms

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Corresponding Author: Juan Rojas Armas, Section of Pharmacology, Faculty of Medicine, Research Clinical Institute, National University of San Marcos, Lima-Peru Tel: 51997251044

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Banisteriopsis caapi, known as "ayahuasca" is a liana of the *Malpighiaceae* family. From the bark are extracted psychoactive constituents that are used in the traditional medicine by healers and shamans from the Amazon countries as Peru, Brazil, Ecuador, Venezuela, Colombia and Bolivia. The mixture of the decoction, infusion or marinated with *Diplopteris cabrerana* leaves (vernacularly called "chaliponga"), releases psychoactive principles with psychological and pharmacological effects[1,2]. The ayahuasca relaxing effects are due to their chemical components as harmine, harmaline, tetrahydroharmine and agenin. The N, N-Dimethyltryptamine (DMT) of chapilonga has psychotropic activity and responsible for the hallucinogenic effect which acts on receptor 5-HT2A, altering brain functions, the perception and inducing visions during the ritual[3,4].

In ethnomedicine, ayahuasca is a potion that is prepared with the mixture of more than 20 plants. However, usually is made with only two species: *Psychotria viridis* (Rubiaceae) and *Diplopteris cabrerana*[5]. This is *Malpighiaceae* family, is a liana from the rain forest in the American continent and is commonly used in infusions with ayahuasca. Although DMT is the majority compound in its chemical composition; it also contains 5-Methoxy-N, N-dimethyltryptamine (5-MeO-DMT) and N, N-Dimethyl-5-hydroxytryptamine (bufotenine).

The amazonian drink ayahuasca was used traditionally for ritual, religious and healing purposes. Its use has been extended to others countries by the globalization[6] and currently is being increasingly used for recreational purposes in USA and Europe[7]. This study in an animal model will set a precedent in the research and contribute scientific support to the preclinical studies that will serve as a basis for future research that seeks to elucidate the effects of ayahuasca and its clinical application. The goal of this work was to observe the effects of *Banisteriopsis caapi* and *Diplopteris cabrerana* on brain, liver, cerebellum and aorta rats, also to assess the psychoactive effects by ingestion of these plant extracts.

MATERIALS AND METHODS

The study was carried out at 2016 January-December.

Plants collection and extraction: *Banisteriopsis caapi* and *Diplopteris cabrerana* were collected in the town of San Juan, district Tiger River, department Loreto, Peru. It was at 240 m above sea level. The sample was taxonomically classified following the phylogenetic criteria according to the APG (Angiosperm Phylogenetic Group) system compared to the Cronquist system[8].

The extract was obtained from ayahuasca bark and chaliponga leaves, separately. The vegetal materials were subject to a process of maceration by 7 days with 96% ethanol at room temperature. After, was filtered, concentrated using a rotary evaporator (BÜCHI Laboratory Technology AG, Flawil Switzerland)and stored in amber color jars at 4°C. The extracts were mixed, with distilled water, in relationship 3 of ayahuasca/7 of chaliponga.

Preliminary phytochemical characterization: The secondary metabolites extracts characterization was made by the application of specific staining and precipitation reagents. To alkaloids: Dragendorff, Mayer, Bertrand and Wagner; anthraquinones: Bortranger; triterpenoids and steroids: Bouchardat; ferric chloride: Phenols; gelatin: Tannins; Shinoda: Flavonoids and foam: Saponins[4,9].

Experimental animals: Thirty five adult female *Rattus norvegicus* Holtzman strain rats were used, with 250 g average weight and obtained from the National Institute of Health, Peru. Rats were exposed to a standard 12/12 light/dark cycle, at room temperature for 2 weeks prior to the experiments with food and water *ad libitum*.

Administration of extracts: The rats were distributed in seven groups (G) of five animals each one. GI:control. GII: 2.5 mL solution of diazepam. GIII: 0.7 mL solution of *Banisteriopsis caapi*. GIV: 0.7 mL solution *Diplopteris cabrerana*. Then GV: 0.7 mL, GVI: 3.5 mL and GVII: 7.0 mL of an extract of *Banisteriopsis caapi* and *Diplopteris cabrerana*.

All extracts were administered two times a week for a month.

Macroscopic evaluation: The groups intervened were subjected to observation to motor activity and psychoactive effects, reflections, sedation, drowsiness, passivity, facial tremors, vigil, diuresis and response to touch[10].

Microscopic evaluation: After 24 h of the last treatment with extracts the animals were sacrificed by cervical dislocation. After, brain, cerebellum, liver, aorta removed and immersed in 10% formalin solution for fixation until histopathological analysis. The 2 µm of thickness samples were obtained with microtome (Ernst Leitz Wetzlar, Ontario Canada), were

dehydrated, treated with paraffin, stained with hematoxylin-eosin (HE) and observed under a microscope Leica DME (Leica Microsystems, Wetzlar Germany) dual-head light. Microscopic observations were performed at 100× and 400× magnification. Four fields were used to count cells at 400× magnification. The results are present as average. The samples were evaluated by an expert and the team's work.

Animal experiments were conducted according to guidelines of the Committee of ethics of the School of Pharmacy and Biochemistry-National University of San Marcos-Lima.

Statistical analysis: The data were analyzed using the Chi-square test. Fisher's exact test was used to determine the significance between the control group and each treated group. In all cases the difference was considered statistically significant when $p<0.05$. The statistical package used was statistical package for social sciences (SPSS) version 20[11].

RESULTS

Phytochemical characterization: The characterization of secondary metabolites by several reagents confirmed the presence majority of alkaloids in the extracts of *Banisteriopsis caapi* and *Diplopteris cabrerana*, as is shown in Table 1.

Macroscopic evaluation: Psychoactive effects were evaluated. Both extracts separately produced litter effects. However, the mix of both extracts produced effects dose dependent. In GVII, that received 7 mL of the mixture of *Banisteriopsis caapi*+*Diplopteris cabrerana*, it is noted passivity, reduced motor activity, lost drive of lower members, strong seizures, facial tremors, diuresis, irritability and spasms, as shown in Table 2.

Microscopic evaluation: The effect of brain extracts showed slight alterations as are duction of neurons and glial cells and discreet edema only with higher doses of the ayahuasca-chaliponga mixture. Cerebellum is not showed alterations just with ayahuasca. While with chaliponga is observed discrete cortical edema and decrease the number of granulose cells. Ayahuasca-chaliponga mixture in lower doses produced Purkinje cells with poikilocytosis and decreased a numberof neurons and glial cells. Discreet edema and reduction of Purkinje cells number were observed with higher doses. The most affected organ was liver with structural disorder produced by both ayahuasca and chaliponga; while with mixture ayahuasca-chaliponga the effects increased as the dose increases. This was also showed vacuolated hepatocytes, fatty liver, congestion, micro-vascularization, inflammation, increased number of Kupffer cells and lysis. There were not changes with chaliponga in aorta but with ayahuasca occurred. These changes increased with ayahuasca-chaliponga mixture achieving greater insult with the highest dose. The abundance of lipophages and endothelial dysfunction is observed. All these results are shown in Table 3, Fig. 1.

Table 1: Screening of phytochemical extracts of *Banisteriopsis caapi* and *Diplopteris cabrerana*

Reagents	Metabolites	*Banisteriopsis caapi*	*Diplopteris cabrerana*
Dragendorff	Alkaloids	++++	++++
Mayer	Alkaloids	++++	++
Bertrand	Alkaloids	++++	+
Wagner	Alkaloids	+++	++
Bortranger	Anthraquinones	+++	+++
Bouchardat	Triterpenoids and steroids	++++	+++
Ferric chloride	Phenolics	++	++++
Gelatin	Tannins	-	-
Shinoda	Flavonoids	++++	+++
Foam	Saponins	++++	+++

High evidence (++++), medium evidence (+++), insufficient evidence (++), non-evidence (-)

Table 2: Psychoactive effects of the extracts of *Banisteriopsis caapi* and *Diplopteris cabrerana* in rats

Groups (G)	Macroscopic analysis
G-I control	Natural behavior, spontaneous motor activity, normal reflexes
G-II Diazepam 2.5 mL	Sedation, drowsiness, squeals, passivity, straight motor activity
G-III *Diplopteris cabrerana* 0.7 mL	Passivity, natural reflexes, mild sedation
G-IV *Banisteriopsis caapi* 0.7 mL	Reduced motor activity, mild sedation, passivity, response to touch
G-V *Banisteriopsis caapi*+*Diplopteris cabrerana* 0.7 mL	Vigil, drowsiness, educed motor activity, passivity, facial tremors, sedation
G-VI *Banisteriopsis caapi*+*Diplopteris cabrerana* 3.5 mL	Reduced motor activity, facial tremors, diuresis
G-VII *Banisteriopsis caapi*+*Diplopteris cabrerana* 7.0 mL	Passivity, mild seizures, motor loss of lower limbs, reduced motor activity, facial tremors, diuresis, drowsiness, vigil

Table 3: Effects of the extracts of *Banisteriopsis caapi* (ayahuasca) and *Diplopteris cabrerana* (chaliponga) on rats organs

Groups	Brain	Cerebellum	Liver	Aorta
G-I Control	Normal	Normal	Normal structure	Normal
G-II Diazepam 2.5 mL	Normal	Decrease the number of neurons and Purkinje cells Increase of glial cells	Mild congestion Structural disorder Vacuoles	Normal
G-III Ayahuasca 0.7 mL	Normal	Normal	Mild congestion Structural disorder	Wall aortic thick with lipophage
G-IV Chaliponga 0.7 mL	Normal	Mild cortical edema Decrease the number of granule cells	Structural disorder	Normal
G-V Ayahuasca+Chaliponga 0.7 mL	Normal	Purkinje cells with poikilocytosis (in orientation and form)	Structural disorder Vacuoles in hepatocytes Congestion Hepatic steatosis Microvacuoles Fatty liver	Lipophages Decrease endothelial thickness Loss of elasticity
G-VI Ayahuasca+Chaliponga 3.5 mL	Decrease of the number of neurons and glial cells	Decrease the number of neurons and glial cells	Structural disorder Vacuoles in hepatocytes Fatty liver Apoptotic cells Steatosis Veins with blood Congestion Microvascularization Inflammation Increase number of kupffer cells Lysis/fatty liver	Wall aortic thick Lipophages
G-VII Ayahuasca+Chaliponga 7 mL	Mild edema	Mild edema and decrease the number purkinje cells	Hepatocyte-toxic Lysis/hepatic steatosis Fatty liver	Aorta with abundant lipophages Endothelial dysfunction (loss of elasticity)

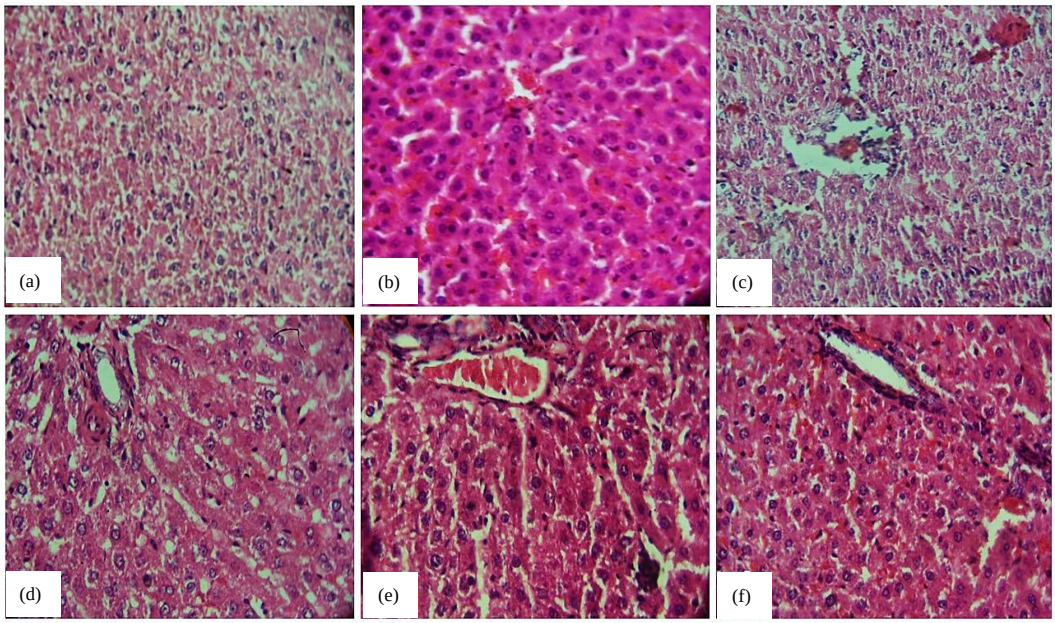

Fig. 1: Effects of the extracts of *Banisteriopsis caapi* and *Diplopteris cabrerana* on hepatic tissue. a. Control: Normal hepatocytes without vascularization. b. Ayahuasca 0.7 mL: sinusoidal channels congestion and hemorrhage in liver. c. Chaliponga 0.7 mL: Steatosis and Increase number of Kupffer cells. d. Ayahuasca+Chaliponga 0.7 mL: Structural disorder, Fatty liver (large vacuoles), Increase number of Kupffer cells. e. Ayahuasca+Chaliponga 3.5 mL: Fatty liver, Structural disorder, Increase number of Kupffer cells. f. Ayahuasca+Chaliponga 7 mL: Hepatocyte-toxic, lysis/ steatosis, fatty liver. Microscopic observations are in 400× magnification

DISCUSSION

The mixture of *Banisteriopsis caapi* and *Diplopteris cabrerana* produces ahallucinogenic effect; doesn't effect when are taken separately. The chemical constituents of the ayahuasca are inhibitors of the enzyme monoamine oxidase (MAO), which is metabolized and broken down simple amines such as N, N-Dimethyltryptamine (DMT). This is a component of chaliponga, responsible for the effect of hallucinogen when consumed orally[12]. The dopamine also is metabolized by the MAO, but the ayahuasca decreases its metabolism, then the effect of the dopamine increases. It was observed that mixture increases the diuresis in rats. This would be due to the effect of dopamine on D_1 receptors, which, at the level of the renal tubule, inhibits the reabsorption of Na^+ and increases diuresis[13].

Studies of these psychotropic plants and their physiological and psychological effects have motivated us to investigate its psychoactive, organic and toxic effects on rats. There are studies in adolescent exposure to ayahuasca in a religious context, where no reported psychiatric problems or neuropsychological[14]. Another study in ayahuasca users also showed no evidence of psychological maladjustment, impaired mental health or cognitive impairment[15]. But there are toxic effects of ayahuasca when is chronically administered, in pregnant rats the effect depending on the plant species and the doses administered[16]. It has also been shown in humans that ayahuasca produces neurophysiological and visual effects by 5-HT_{2A} receptor activation[17].

The cause of the death of a 25 years man was caused by the consumption of an extract of herbs containing ayahuasca, in it was found, the hallucinogenic amine of 5-Methoxy-N, N-dimethyltryptamine as a causative agent of poisoning and death[18]. In the study of the mixture of ayahuasca and chaliponga is necessary to know its Pharmacology and possible toxicity for human consumption. Ingestion may cause chronic and acute effect; more even when it is associated with other species that enhance its hallucinogenic or toxic effect. Its use may be possible in the pharmacological treatment of dependent drugs as alcoholism and depression. Likewise, may be possible in the treatment of cancer, Alzheimer's and Parkinson's diseases[19]. The potential of ayahuasca and the poison or lethal effects that may occur with other drugs of different species with which it is mixed gives us information about the mechanisms of this plant. Adverse reactions and methodologies for the ayahuasca's preparation would provide us forensic and toxicological data of its effects and chemical composition[20].

In the development of this pharmacological model of psychoactive effects and organic botanical species studied in rats, it is necessary to emphasize the few studies of these effects at the level of the aorta and liver. The preparation of the ayahuasca potion contains different concentrations of psychotropic agents. It is reported that each milliliter of Peruvian ayahuasca contains 0.6 mg of DMT[21], also were studied the effects of ingestion of ayahuasca and its effects on the level of certain neurotransmitters and the use of monoamines in the hippocampus and amygdalein healthy rats[22]. Studies of the consumption of the ayahuasca potion suggest that is well tolerated, including its use chronic and not existing information on their toxicity in human[23]. However, in this study, performed in healthy rats and observed microvascularizations and lipophages in the aorta, also structural disorder in the liver.

In a study conducted in rats Wistar females, when was administered an infusion of ayahuasca orally for 14 days, was observed abnormal neuronal activity, toxicity in the caudate nucleus and hippocampus. Not evaluated the lethal dose but was the highest dose (30x the dose used in rituals). Likewise, there were antidepressant effects in rats at high doses[24]. These effects are in line with this study, since increasing doses of ayahuasca-chaliponga mixture, increased the structural disorder of liver tissue, steatosis, congestion, also, microvasculature and endothelial dysfunction in the aorta. Also,was observed an intense antidepressant effect which should be investigated. Animal studies have shown theantidepressant and anxiolytic effect of ayahuasca, harmine and harmaline. Likewise, human studies also suggest that the ayahuasca is associated with areduction of the symptoms of anxiety and depression[25].

This study focused on a phenomenon of interest to the clinical and social psychology which is justified with the results obtained. Also, the attention to native plants in their ancestral use by ethnic groups in our Amazon, seeking to provide explanations that guide the use of these plants with better knowledge and applications in the field of medicine, pharmacology, toxicology and pharmaceutical industry.

This research implies a greater pharmacological and toxicological knowledge of ayahuasca necessary for the development of future preclinical or clinical studies. The therapeutic applications of ayahuasca, attributed to harmine, are due to its vasorelaxant, anti-inflammatory, analgesic, antimicrobial, antioxidant, antiparkinsonian, antitumor, anti-addictive and antidepressant properties. Although there is evidence that harmine is useful for treating Parkinson's symptoms, such as muscle stiffness, depression, memory deficit, apathy, phobias, fatigue and attention problems, ayahuasca has other components that include β-carbolines, It is recommended to explore the therapeutic properties of this natural alkaloid in depth. One of the limitations of this research is that the methodology focuses exclusively on an animal model and it is unknown if the results can be extrapolated to humans; Also, the doses of these preparations are unknown, which can be very different for animals and for people.

CONCLUSION

From the results of this study, it is deduced that the mixture of *Banisteriopsis caapi*+*Diplopteris cabrerana* ethanolic extracts exerts psychoactive and organic effects in rats. It is suggested to continue research in this field to learn more about the effects of these native plants.

SIGNIFICANCE STATEMENTS

This study discovers the effects of high doses of the mixture of the ethanol extracts of *Banisteriopsis caapi* and *Diplopteris cabrerana* in a murine model. This study demonstrates the potential to cause significant psychoactive effects as well as hepatic and aortic alterations. This study will help the researcher to uncover the critical area of ayahuasca pharmacology and toxicology that many researchers were not able to explore. Thus, new theories can be discovered on the effects of the different combinations that are used in the preparation of ayahuasca.

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