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# Gas Chromatographic Analysis of Dimethyltryptamine and β-Carboline Alkaloids in Ayahuasca, an Amazonian Psychoactive Plant Beverage

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**ABSTRACT:**
**Introduction – Ayahuasca is obtained by infusing the pounded stems of *Banisteriopsis caapi* in combination with the leaves of *Psychotria viridis*. *P. viridis* is rich in the psychedelic indole *N,N*-dimethyltryptamine, whereas *B. caapi* contains substantial amounts of β-carboline alkaloids, mainly harmine, harmaline and tetrahydroharmine, which are monoamine-oxidase inhibitors. Because of differences in composition in ayahuasca preparations, a method to measure their main active constituents is needed.**
**Objective – To develop a gas chromatographic method for the simultaneous determination of dimethyltryptamine and the main β-carbolines found in ayahuasca preparations.**
**Methodology – The alkaloids were extracted by means of solid phase extraction ($C_{18}$) and detected by gas chromatography with nitrogen/phosphorous detector.**
**Results – The lower limit of quantification (LLOQ) was 0.02 mg/mL for all analytes. The calibration curves were linear over a concentration range of 0.02–4.0 mg/mL ($r^2 > 0.99$). The method was also precise (RSD < 10%).**
**Conclusion – A simple gas chromatographic method to determine the main alkaloids found in ayahuasca was developed and validated. The method can be useful to estimate administered doses in animals and humans for further pharmacological and toxicological investigations of ayahuasca. Copyright © 2009 John Wiley & Sons, Ltd.**

**Keywords:** Dimethyltryptamine; β-carbolines; ayahuasca; gas chromatography

## Introduction

Ayahuasca, also known by the names Hoasca, Daime, Yajé, Natema and Vegetal, is a psychoactive plant tea originally used by shamans throughout the Amazon Basin in magico-religious practices and folk medicine of indigenous people (Riba *et al*., 2003). This beverage is obtained by infusing the pounded stems of *Banisteriopsis caapi* in combination with the leaves of *Psychotria viridis*. *P. viridis* contains the psychedelic agent *N,N*-dimethyltryptamine (Fig. 1), whereas *B. caapi* contains β-carbolines such as harmine, harmaline and tetrahydroharmine (Fig. 1), which are potent monoamine oxidase (MAO) inhibitors. Dimethyltryptamine is not orally active itself because it is inactivated by peripheral MAO (present in liver and gut). However, the inhibition of MAO by β-carbolines allows the oral activity of dimethyltryptamine, enabling it to reach its site of action in the central nervous system. The synergistic interaction of these alkaloids is the basis of the psychotropic action of ayahuasca (McKenna, 2004).

In Brazil, ayahuasca has been incorporated in rituals of modern syncretic religious groups, mainly the Santo Daime and the União do Vegetal (UDV), where the beverage is reported to be used to facilitate self-knowledge and introspection. In 2004, the use of ayahuasca within religious context was officially recognised and

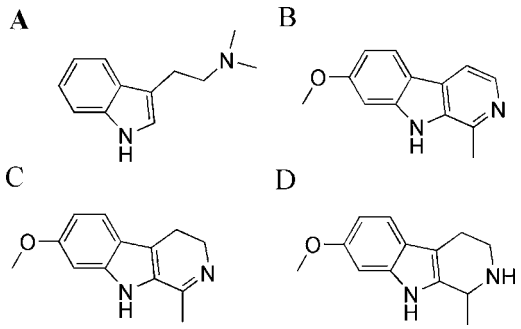


**Figure 1.** Chemical structures of the main ayahuasca alkaloids: (A) dimethyltryptamine, (B) harmine, (C) harmaline and (D) tetrahydroharmine.

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protected by law in Brazil (Conselho Nacional Antidrogas Brasil, 2004), the only country where it currently enjoys legal protection, analogous to the status held by the Native American Church for the use of peyote (*Lophophora williamsii*) in the United States.

In recent years, the use of ayahuasca has spread outside South America and some religious groups have established in the United States and in several European countries (Riba *et al*., 2001). As an increasing number of people have come into contact with this psychotropic tea, the beverage has begun to attract the attention of researchers interested in its pharmacological and toxicological aspects (Gable, 2007; Callaway *et al*., 1999; Callaway, 2005; Riba and Barbanoj, 2005; Riba *et al*., 2003).

Peruvian ayahuasca (100 mL) has been shown to contain dimethyltryptamine (60 mg), harmine (467 mg), harmaline (41 mg) and tetrahydroharmine (160 mg) using two-dimensional thin-layer chromatography, high-performance liquid chromatography and gas chromatography–mass spectrometry (McKenna *et al*., 1984), whereas Brazilian ayahuasca (100 mL) has been shown to contain 24, 170, 20 and 107 mg respectively of the same four alkaloids using gas chromatography and high-performance liquid chromatography (Callaway *et al*., 1996).

No detailed analytical procedure seems to have been previously reported for the simultaneous quantification of these alkaloids in ayahuasca tea. Usually, dimethyltryptamine is determined by gas chromatography using a nitrogen–phosphorous detector (GC-NPD) and $\beta$-carbolines by high-performance liquid chromatography (HPLC) in different procedures (Callaway *et al*., 1996, 1999; Yritia *et al*., 2002). However, Kikura-Hanajiri *et al*. (2005), simultaneously detected some hallucinogenic tryptamines/$\beta$-carbolines, including dimethyltryptamine, harmine and harmaline, using gas chromatography-mass spectrometry (GC-MS) or liquid chromatography–electrospray ionisation–mass spectrometry (LC-ESI-MS).

In the present work, a method for simultaneous determination of the main active constituents found in ayahuasca was developed and validated. Solid-phase extraction (SPE) and gas-chromatography with a nitrogen–phosphorous detector (GC-NPD) was used to purify and quantify the analytes. The developed method can be useful to estimate administered doses in animals and humans for further pharmacological and toxicological investigations of ayahuasca.

## Experimental

**Reagents and chemicals.** Sodium borohydride, sodium borate, HPLC-grade methanol and acetonitrile were purchased from Merck (Darmstadt, Germany). Classic Sep-Pack® $C_{18}$ cartridges (360 mg) were purchased from Waters Co. (Bellefonte, PA, USA). Diphenhydramine, tryptamine, harmine hydrochloride and harmaline hydrochloride were purchased from Sigma Co. (St Louis, MO, USA). Eight samples of different ayahuasca preparations were obtained from a religious group settled in the city of Araçoiaba da Serra, São Paulo state, Brazil.

**Synthesis of tetrahydroharmine.** The synthesis of tetrahydroharmine was performed according to the procedure described by Callaway *et al*. (1996). In summary, harmaline hydrochloride (251 mg, 1.0 mmol) was slowly added to a methanolic sodium borohydride solution (38 mg, 1.0 mmol) at 0°C. After 40 min, the reaction mixture was acidified with HCl (1 M, 5.0 mL), then alkalised with NaOH (5% m/v, 10 mL) and extracted with dichloromethane (2 × 20 mL). The organic layer was dried with magnesium sulfate, filtered and evaporated under vacuum. The evaporated residue was twice recrystallised with ethanol (20 mL), generating off-white crystals with a melting point of 197°C. The structure was confirmed on the basis of the $^1$H NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 1.36 (3H, d, $J$ = 7.21, NHCHC***H***$_3$); 2.66 (2H, t, $J$ = 7.23, C***H***$_2$CH$_2$NH); 2.96 (2H, t, $J$ = 7.22, CH$_2$C***H***$_2$NH); 3.27 (1H, q, $J$ = 7.23, NHC***H***CH$_3$); 3.76 (3H, s, OC***H***$_3$); 6.69 (1H, d, $J$ = 6.8, Ph); 6.76 (1H, s, Ph); 7.27 (1H, s, Ph); and ESI-MS ($m/z$) data: 217 $[M + H]^+$; 201$[M - CH_3 + H]^+$; 185 $[M - OCH_3 + H]^+$.

**Synthesis of dimethyltryptamine.** The synthesis of dimethyltryptamine was performed according to a modified procedure based on the selective dimethylation method described by Giumanini *et al*. (1980). Sodium borohydride (57 mg, 1.5 mmol) was slowly added to a stirred solution of tryptamine (160 mg, 1.0 mmol) in tetrahydrofuran at 0°C. Afterwards, sulfuric acid (2 M, 5.0 mL) and an aqueous solution of formaldehyde (40% v/v, 2.0 mL) were also added. This solution was diluted with water and alkalinised with NaOH pellets until pH 14 was reached. The obtained product was extracted with diethyl ether (3 × 20 mL). The organic layer was dried with magnesium sulfate, filtered and evaporated under vacuum. The product was purified by means of a silica chromatographic column (eluted with *n*-hexane–ethyl acetate 80:20) and recrystallisation with *n*-hexane–ethyl acetate (80:20). White crystals with a melting point of 64°C were obtained with this procedure. The structure was confirmed on the basis of the $^1$H NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 2.26 [s, 6H, N(C***H***$_3$)$_2$]; 2.55 [t, 2H, $J$ = 7.22, C***H***$_2$CH$_2$N(CH$_3$)$_2$]; 2.63 [t, 2H, $J$ = 7.23, CH$_2$C***H***$_2$N(CH$_3$)$_2$]; 7.3–7.5 (m, 4H, Ph); 7.2 (s, 1H, C=–***H***); and ESI-MS ($m/z$) data: 189 $[M + H]^+$; 145 $[M - N(CH_3)_2 + H]^+$; 117 $[M - (CH_2)_2N(CH_3)_2 + H]^+$.

**Preparation of standard solutions.** Stock solutions (10 mg/mL) of dimethyltryptamine, harmine, harmaline and tetrahydroharmine were each prepared with methanol in volumetric glassware. Stock standard solutions were stable for at least 30 days when stored in the freezer at −20°C. The stability was checked by preparing a new stock standard solution and comparing the detector responses obtained from freshly prepared dilutions of old and new stock standard solutions. Working solutions at concentrations of 1 mg/mL were also prepared in methanol by diluting stock solutions.

**GC-NPD analyses.** Analyses for dimethyltryptamine, harmine, harmaline and tetrahydroharmine were performed using an Agilent gas chromatograph model 6890 equipped with a nitrogen–phosphorous detector and 7683 series automatic injector (Little Falls, DE, USA). Chromatographic separation was achieved on an HP Ultra-2 fused-silica capillary column (25 m × 0.2 mm × 0.33 μm film thickness) using ultra-pure-grade nitrogen as carrier gas at 0.6 mL/min in a constant flow rate mode. Injections (1 μL) were made in split mode (ratio 1:20). The injector port and detector temperatures were 200 and 250°C respectively. The oven temperature was maintained at 150°C for 1 min; programmed at 10°C/min to 250°C with a hold at 250°C for 7 min.

**Ayahuasca sample extraction.** A sample solution containing ayahuasca (0.5 mL), borate buffer (pH 9.0, 3.0 mL) and the internal standard diphenhydramine (100 μL of a solution of 1.0 mg/mL) was loaded onto a $C_{18}$ cartridge mounted on a vacuum manifold and conditioned with methanol (2.0 mL), deionised water (1.0 mL) and borate buffer (pH 9.0, 2.0 mL). The loaded cartridge was

further washed with deionised water (1.0 mL) and with a solution of acetonitrile–water (1:9, 1.0 mL). After drying the cartridges under full vacuum for 7 min, the elution of analytes was performed with methanol (2.0 mL). Of this solution, 1 μL was injected in the GC-NPD system. The analytes were identified based on comparison of its relative retention time with the corresponding values of standards assayed in the same run. Quantification was based upon the ratio of the integrated peak area to the internal standard.

**Limit of detection (LOD) and lower limit of quantification (LLOQ).** The LOD and LLOQ were determined by an empirical method that consisted of analyzing a series of water samples containing decreasing amounts of the dimethyltryptamine, harmine, harmaline and tetrahydroharmine (Armbruster *et al*., 1994). The LOD was the lowest concentration that presented an RSD that did not exceed 20% and the LLOQ the lowest concentration that presented na RSD that did not exceed 10% in six replicates.

**Recovery.** The recovery efficiency of the SPE method was evaluated by analyzing two sets of samples. Set A consisted of three concentrations each of dimethyltryptamine, harmine, harmaline and tetrahydroharmine, i.e. 0.3, 1.5 and 3.0 mg/mL, corresponding to the expected alkaloid concentrations in ayahuasca and each extracted as described, i.e. the processed samples. The analyses were performed in six replicates for each concentration. Sample set B was analysed in an identical manner except that the alkaloid standards, at the same concentrations, were added to the matrix after the SPE phase, i.e. the unprocessed samples. The unprocessed response represented 100% recovery. To both sets, internal standards were added prior to the extraction of the sample. The absolute recovery was evaluated by comparison of the mean response of alkaloids in the processed samples with those in the unprocessed samples.

**Linearity.** Aqueous samples of each of the alkaloids at 0.02, 0.1, 0.5, 1.0, 2.0 and 4.0 mg/mL were analysed in triplicate to assess linearity of response.

**Intra- and inter-assay precision.** Precision, defined as the relative standard deviation (RSD) or coefficient of variation (CV), was determined by analysing aqueous solutions of dimethyltryptamine, harmine, harmaline and tetrahydroharmine in the concentrations of 0.3, 1.5 and 3.0 mg/mL on three different days. The analyses were carried out in six replicates for each concentration and each day.

**Accuracy.** The accuracy of the entire SPE and GC-NPD method was evaluated by analysing, in triplicate, aqueous solutions of dimethyltryptamine, harmine, harmaline and tetrahydroharmine in the concentrations of 0.3, 1.5 and 3.0 mg/mL. The experimental concentrations, quantitated using the standard calibration curves, were then expressed as a percentage of the known concentration, i.e. mean measured concentration/nominal concentration × 100.

**Stability.** The stabilities of the analytes in an ayahuasca sample and a spiked water sample (1.5 mg/mL of each analyte) were evaluated after 24 h at room temperature. The stabilities of analytes in extract samples on the carrousel were evaluated over an 8 h period. Stability tests were performed in triplicate.

## Results and Discussion

The ayahuasca beverage is unique among plant hallucinogens as its psychotropic activity is dependent on the synergistic interaction of the alkaloids present in two plants, i.e. *Banisteriopsis caapi* and *Psychotria viridis*. In recent years, an increasing interest has been observed in the scientific study of ayahuasca, including its botany, chemistry, pharmacology and toxicology. Since the basis for pharmacological and toxicological investigations is the qualitative and quantitative characterisation of its active constituents, a method was developed and validated for the determination of the main alkaloids, dimethyltryptamine, harmine, harmaline and tetrahydroharmine, found in ayahuasca samples. The method was based on the procedure described by Yritia *et al*. (2002) for the detection of β-carbolines in plasma samples using SPE and HPLC. In the current study, dimethyltryptamine could be extracted under the same conditions as those suitable for β-carbolines and analysed by GC-NPD.

Calibration curves were linear over the specified range (0.02–4.0 mg/mL). The linear regression equations and coefficients of correlation were: dimethyltryptamine ($y = 8.9651x - 0.6738$; $r^2 = 0.9971$); harmine ($y = 3.9346x - 0.5288$; $r^2 = 0.9946$); harmaline ($y = 1.7309x + 0.0057$; $r^2 = 0.9956$) and tetrahydroharmine ($y = 10.052x - 1.5445$; $r^2 = 0.9941$), where $y$ and $x$ represent the relationship between the peak area ratio (compound/internal standard) and the corresponding calibration concentrations, respectively.

The confidence parameters of the validated method (LOD, LLOQ, recovery, accuracy and intra- and inter-assay precision) for the determination of dimethyltryptamine, harmine, harmaline and tetrahydroharmine are shown in Table 1. Quantitative analysis indicated that analytes were stable in ayahuasca and in water at room temperature for 24 h since losses of analytes < 10% were observed. Analytes were also stable on the sample extracts after 8 h on the carrousel.

The method showed good linearity over a broad concentration range (0.02–4.0 mg/mL). The precision varied slightly indicating that the reproducibility is acceptable over the studied concentration range (CV < 10%). The solid-phase extraction (SPE) procedure produced clean extracts with good recovery (better than 68%). Good sensitivity was also obtained for all analytes (LLOQ = 0.02 mg/mL) using low volume of sample (0.5 mL).

The analytical method was applied to eight different ayahuasca preparations (Table 2). Typical GC-NPD chromatograms resulting from the analysis of an aqueous sample containing 0.5 mg/mL of each alkaloid and from an ayahuasca sample (sample 2, Table 2) derived from a religious group settled in Araçoiaba da Serra city, Brazil are shown in Fig. 2. Different concentrations were found among batches of ayahuasca, despite having the same origin. The discrepancy in alkaloid concentration can be explained by the different methods of preparation as well as the amounts and proportions of the source plants (McKenna, 2004). Also, alkaloid concentrations can vary considerably among plants and consequently the ayahuasca prepared with them (McKenna *et al*., 1984). Therefore, depending on all these factors, different ayahuasca preparations can produce variable intensity in psychotropic response.

Although the described method is suitable for the reliable determination of dimethyltryptamine and some β-carboline alkaloids found in ayahuasca teas, the lower limits of quantification obtained do not allow its use to quantify these compounds in human plasma samples after an ayahuasca ingestion.



  

**Table 1.** Confidence parameters of the validated method for the determination of dimethyltryptamine, harmine, harmaline and tetrahydroharmine in ayahuasca samples

| | Dimethyl-tryptamine | Harmine | Harmaline | Tetrahydro-harmine |
|---|---|---|---|---|
| LOD (mg/mL) | 0.01 | 0.01 | 0.01 | 0.01 |
| LLOQ (mg/mL) | 0.02 | 0.02 | 0.02 | 0.02 |
| Recovery (%) | | | | |
| C1 | 89.9 | 70.4 | 92.8 | 87.4 |
| C2 | 78.7 | 87.8 | 95.9 | 99.0 |
| C3 | 81.7 | 82.9 | 68.4 | 84.5 |
| Intra-assay precision (RSD, %) | | | | |
| C1 | 3.6 | 9.4 | 9.5 | 8.7 |
| C2 | 2.6 | 2.3 | 6.5 | 8.9 |
| C3 | 1.9 | 1.3 | 9.7 | 2.4 |
| Inter-assay precision (RSD, %) | | | | |
| C1 | 7.6 | 8.2 | 8.2 | 5.7 |
| C2 | 6.3 | 2.2 | 6.4 | 1.4 |
| C3 | 9.5 | 8.8 | 6.3 | 4.1 |
| Accuracy (%) | | | | |
| C1 | 95,5 | 105,4 | 94,0 | 102,6 |
| C2 | 101,0 | 97,7 | 105,0 | 99,1 |
| C3 | 99,6 | 100,5 | 97,1 | 100,2 |

LOD = limit of detection; LLOQ = limit of quantification; C1 = 0.3 mg/mL; C2 = 1.5 mg/mL; C3 = 3.0 mg/mL; RSD = relative standard deviation.

**Table 2.** Concentrations of alkaloids dimethyltryptamine, harmine, harmaline and tetrahydroharmine found in ayahuasca samples ($n = 3$)

| Sample number | Concentration (mg/mL) | | | |
|---|---|---|---|---|
| | Dimethyltryptamine | Harmine | Harmaline | Tetrahydroharmine |
| 1 | 0.42 ± 0.02 | 0.62 ± 0.02 | 1.37 ± 0.06 | 0.35 ± 0.02 |
| 2 | 0.73 ± 0.04 | 0.83 ± 0.05 | 1.72 ± 0.05 | 0.67 ± 0.03 |
| 3 | 0.57 ± 0.03 | 0.61 ± 0.03 | 1.14 ± 0.05 | 0.40 ± 0.02 |
| 4 | 0.61 ± 0.01 | 0.47 ± 0.02 | 0.85 ± 0.04 | 0.40 ± 0.03 |
| 5 | 0.59 ± 0.02 | 0.52 ± 0.03 | 0.92 ± 0.03 | 0.36 ± 0.02 |
| 6 | 0.50 ± 0.01 | 0.44 ± 0.02 | 0.69 ± 0.02 | 0.27 ± 0.02 |
| 7 | 0.54 ± 0.02 | 0.37 ± 0.02 | 0.64 ± 0.02 | 0.21 ± 0.02 |
| 8 | 0.31 ± 0.01 | 0.44 ± 0.02 | 0.75 ± 0.03 | 0.25 ± 0.02 |

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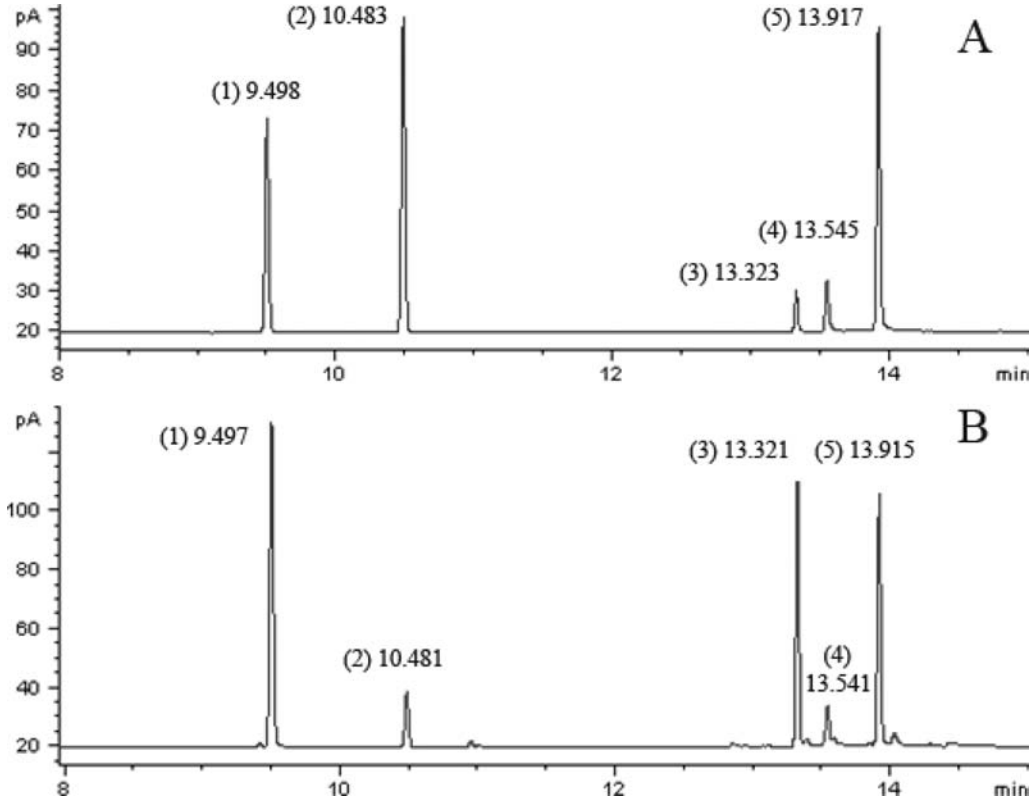


**Figure 2.** GC-NPD chromatograms obtained with the practical use of this method to the analysis of samples: (A) a water sample spiked with 0.5 mg/mL of each alkaloid and (B) an ayahuasca sample (sample 2) deriving from a religious group settled in Araçoiaba da Serra city, Brazil. The analysis revealed the presence of the following concentration: (1) dimethyltryptamine (0.73 mg/mL); (3) tetrahydroharmine (0.67 mg/mL); (4) harmaline (1.72 mg/mL); and (5) harmine (0.83 mg/mL). (2) Peak corresponding to internal standard diphenhydramine.

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