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qNMR: An applicable method for the determination of dimethyltryptamine in ayahuasca, a psychoactive plant preparation

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ABSTRACT

Ayahuasca is an Amazonian plant beverage obtained by infusing the pounded stems of *Banisteriopsis caapi* in combination with the leaves of *Psychotria viridis*. *P. viridis* contains the psychedelic indole *N,N*-dimethyltryptamine (DMT). This association has a wide range of use in religious rituals around the world. In the present work, an easy, fast and non-destructive method by Nuclear Magnetic Resonance of proton (^{1}H NMR) for quantification of DMT in ayahuasca samples was developed and validated. 2,5-Dimethoxybenzaldehyde (DMBO) was used as internal standard (IS). For this purpose, the area ratios produced by protons of DMT ($N(C\mathbf{H}_3)_2$) at 2.70 ppm, singlet, (6*H*) and for DMBO ($Ar(OC\mathbf{H}_3)_2$) at 3.80 and 3.89 ppm, doublet, (6*H*) were used for quantification. The lower limit of quantification (LLOQ) was 12.5 μg/mL and a good intra-assay precision was also obtained (relative standard deviation $< 5.1\%$). The present ^{1}H NMR method is not time consuming and can be readily applied to monitor this tryptamine in plant preparations. We believe that qNMR can be used for identification and quantification of many plant-based products and metabolites with important advantages, while comparing with other analytical techniques.

1. Introduction

Recently, epidemiologic data have alerted scientists around the world about the consumption of a new drink in Europe and the USA, the "Santo Daime's" tea. This is also known as Hoasca, Ayahuasca, Daime, Yajé, Natema and Vegetal. It is a hallucinogenic drink and it is prepared using two different plants: the stems from *Banisteriopsis caapi* and the leaves from *Psycotria viridis* (Callaway et al., 1999). It was originally prepared for magic-religious ceremonies in the Amazon basin (Riba et al., 2003).

P. viridis contains a potent psychedelic agent, *N,N*-dimethyltryptamine (DMT), an indole alkaloid, which is structurally similar to the monoamine neurotransmitter serotonin and acts on receptors 5-$HT_{2A/2C}$ (O'Brien, 1996). Nevertheless, the tea has another active compound, the β-carbolines, which is represented by harmine, harmaline and tetrahydroharmine. They have capacity to inhibit MAO-A, enabling DMT 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, other species also contains this tryptamine in their leaves, such as *Psychotria cartagenensis* and *Diplopterys cabrerana* (McKenna et al., 1984). In the United States, appreciable concentrations of this compound are found in extracts of *Phalaris* (*Phalaris arundinacea*, *Phalaris tuberosa* and *Phalaris aquatica*). There are many other plant sources of this active compound in the region of South America. It can be extracted from seeds of *Anadenanthera peregina* or bark of stems of *Virola* spp. *Mimosa hostilis*, *Lespedeza bicolor*, *Diplopterys cabrerana* (syn. *Banisteriopsis rusbyana*) and *Psychotria viridis* (Thompson et al., 1987).

In the last years, the use of ayahuasca has spread outside South America and some religious groups have established on United States and some European countries (Halpern, 2004). A relative small number of analytical procedures have been reported for evaluation of this compound, which make use of liquid (Callaway et al., 1996) or gas (Gambelunghe et al., 2008; Pires et al., 2009) chromatographic methods and capillary electrophoresis (Huhn et al., 2005).

The aim of this study was the implementation of an alternative method to detect and quantify DMT by Nuclear Magnetic Resonance (NMR) with some advantages in relation of chromatographic methods generally used for the determination of plant metabolites. Therefore, a procedure by ^{1}H NMR was

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developed and validated. This method can be useful to estimate administered doses in animals and humans for further pharmacological and toxicological investigations of ayahuasca. Like demonstrated in this paper, it is possible to use the qNMR concept for the analyses of plant-based products with reproducibility.

2. Results and discussion

The application of qNMR concept for natural products was described (Pauli, 2001). This technique can offer some major advantages in comparison with chromatographic methods. Some information about chemical structure can be obtained at the same time while quantitative measurement is performed, while only in chromatographic hyphenated techniques (such as GC–MS or LC–MS) this feature can be provided. This is particularly true for the measurement of ^{1}H signals, especially when dealing with analogues. Additionally, a further advantage of quantitative procedures for NMR is that there is no necessity for clean-up and derivatization steps. The non-destructive nature of this technique make possible that samples can be kept for future analyses and/or confirmations if necessary. However, sometimes the higher quantification limit might be a problem and it depends on each case. A complete review about qNMR comparing with other analytical methods was recently written (Holmes et al., 2006).

In this study, dimethyltryptamine was quantified by ^{1}H NMR after a treatment with a simple liquid–liquid extraction. The extraction conditions evaluated for the ayahuasca tea indicated that hexane was better in relation to chloroform because the second one carried out endogenous compounds that interfered with the analyses. Using hexane, the method was not affected by the constituents of the extract. This could be proved by the application of the method in a real ayahuasca sample.

Different compounds can be directly compared by ^{1}H NMR through integration ratios of their signals. In DMT case we have chosen the highest signal level that was representative of six hydrogen's ($N(C\mathbf{H}_3)_2$), with chemical shift (δ) of 2.70 ppm. This signal, that represent six hydrogens, show a good intensity which lead to increase the sensitivity of the method. The signals used for quantification of both analyte and internal standard do not suffer any interference of possible residual proton of organic solvent ($C\mathbf{H}Cl_3$ at 7.26 ppm).

Dimethoxybenzaldehyde (DMBO) was chosen as internal standard (IS), which was used for this purpose because its spectrum contains signals that do not overlap with the signals of analyzed psychoactive compound. Besides, it presents other advantages: low cost, easy availability, it is soluble in the same solvent of the extraction method and it is not volatile. The internal standard is also stable in the standardized conditions and did not react with other components of the ayahuasca. This was confirmed for the proportional responses between integration values of hydrogen of aldehyde (1**H**) and dimethoxy (6**H**) present in DMBO in the analysis of the real sample. Thus, both methoxy signals with δ of 3.80 and 3.89 ppm were used for quantification. In Fig. 1, it is possible to see the characteristic spectra obtained with the practical use of this method to the analysis of a water sample spiked with dimethyltryptamine and internal standard. In order to take better quality to representative figures showed here, the spectra were processed with MestRec® 4.7.4.0.

Considering that the original goal was to implement a new and easy method that could be employed to analyze DMT in preparations of *P. viridis*, we selected some ayahuasca samples for analyses. In Fig. 2, it can be observed the ^{1}H NMR obtained for ayahuasca tea sample in which internal standard was added. In this specific case, were used 3 mL of tea and 500 μg of IS. With the application of the method, a concentration of 400 μg/mL of *N*,*N*-dimethyltryptamine was obtained. No interference of other

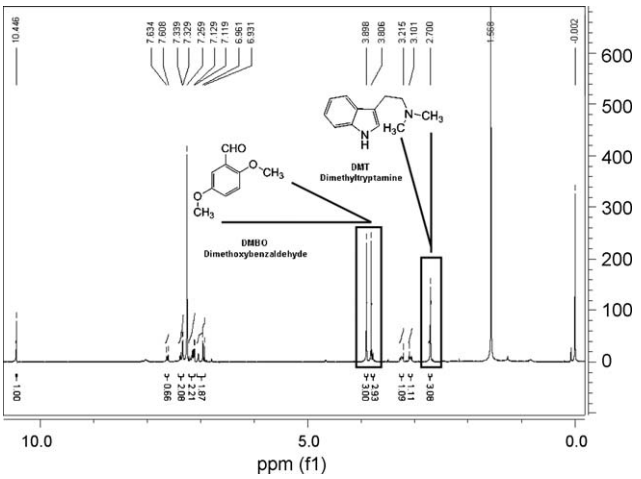


Fig. 1. ^{1}H NMR spectra of a water sample containing *N*,*N*-dimethyltryptamine and internal standard (2,4-dimethoxybenzaldehyde). Signals relative to protons of DMT and DMBO used for quantification are indicated, beyond its chemical shift and signal integration.

constituents of ayahuasca was found in the analysis. This concentration is in accordance with the result obtained by the gas chromatographic method previously published by our research group (Pires et al., 2009) for similar samples. McKenna (2004) also determined concentrations of about 500 μg/mL of this molecule in *P. viridis* preparation depending on its origin.

Quantitative analyses by the ^{1}H NMR technique need some precautions aside from the necessity to adequate the choice of specific signals in the spectrum and NMR parameters. The delay for total relaxation of spins must be observed to be within 0.7% of the maximum that occurs after a time $5T_1$, where T_1 is the spin-lattice relaxation time for a given nucleus. In this procedure, with pulse of 30°, was used 10.0 s, which is considered enough to completely relax all analyzed protons (Saito et al., 2004). Also, signal-to-noise ratio (*S*/*N*) effect has a significant influence in qNMR methods can lead to systematic mistakes. This effect, which is influenced by variations of pulse flip angle, number of scans and the line broadening (lb) can affect strongly the precision of the measurement. The *S*/*N* of at least 150 is required for the target uncertainty of <1% (Malz and Jancke, 2005).

The data processing and integration of the spectra are the potentially most subjective aspect of NMR quantification. Burton

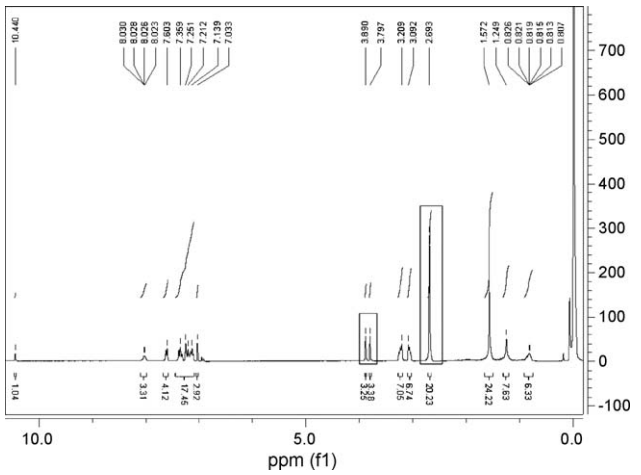


Fig. 2. ^{1}H NMR spectra of an ayahuasca tea sample submitted to the method where internal standard was added. Signals referents of protons of DMT and internal standard used for quantification are indicated.

and colleagues, after comparison between operators for manual integration, reported an error less than 1% (Burton et al., 2005). The errors in case of automatic integration should not be higher that 1%. However, with the evolution of software, equipment and adequate spectral processing such as zero-filling, FID weighting and baseline correction, the NMR signal integration cannot be considered as a principal source of systematic error.

The parameters of validation of quantitative NMR analyses for this compound in ayahuasca using internal standard showed good results. The obtained data are an indicative of robustness and reproducibility of the method in instrumental optimized conditions. The calibration curve was linear over the specified range (25–1000 mg/L). The linear regression equation and coefficient of correlation were: $Y = 8.4713X - 0.1019$, $r^2 = 0.999$, where Y and X represents the relationship between the peak signal ratio (compound/internal standard) and the corresponding calibration concentrations, respectively. In Fig. 3, it is possible to examine the response for three different concentrations of DMT (25, 50 and 100 mg/L) used for calibration curve are showed.

The intra-assay precision varied slightly indicating that the reproducibility is acceptable over the studied concentration range (RSD < 5.1%). Good sensitivity was also obtained for the analyses (LOD and LLOQ = 12.5 mg/L). During the experiments to obtain LOD and LLOQ, it was verified that lower concentrations than 12.5 mg/L, no signal was detected, so we considered this value as being LOD and LLOQ, since the RSD at this concentration was better than 20% (Armbrsuter and Pry, 2008). The recovery was 70% in media for the three concentrations evaluated. The variation of 5% was indicative of reproducibility of the optimized method for sample extraction.

The concentration of psychoactive compound in tea can vary considerably among plants and, consequently, the ayahuasca prepared with them (McKenna et al., 1984). Therefore, depending on every one of these factors, different ayahuasca preparations can produce changeable intensity in psychotropic response.

In conclusion, the results described in this work demonstrate that it is possible to analyze *N*,*N*-dimethyltryptamine, the psychoactive compound presented in the preparation of *P. viridis* (ayahuasca tea) by ^{1}H NMR. The main advantages in comparison with chromatographic methods can be summarized: (i) to be very fast (the NMR measurement can be performed in less than 30 s for sample), do not need extra-time for column equilibration; (ii) do not need extra-reaction (derivatization); (iii) the sample is not destroyed; (iv) give information about chemical structure in the same analyses; (v) have good validation parameters; and (vi) easy sample preparation because its good specificity. This technique can be an efficient tool to monitor the presence of this drug in plant preparation samples. In addition, with the optimization of instrumental parameters, qNMR may be adapted for the analysis of other constituents in plant-based products.

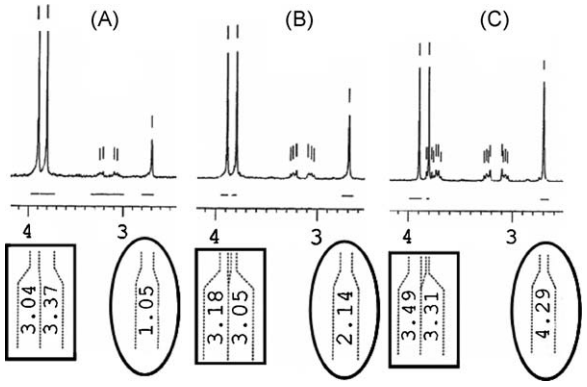


Fig. 3. Three typical ^{1}H NMR used for the determination of linearity with different concentration of dimethyltryptamine: (A) 25 μg/mL; (B) 50 μg/mL; and (C) 100 μg/mL.

3. Materials and methods

3.1. Reagents

The internal standard, 2,5-dimethoxybenzaldehyde (DMBO), and the analytical solvent used for extraction (hexane) were purchased from Sigma–Aldrich Chem. Co. (Milwaukee, WI, USA). The deuterated solvent (chloroform, $CDCl_3$) was purchased by Cambridge Isotope Laboratories (Andover, MA, EUA). *N*,*N*-Dimethyltryptamine is not founded in commercial forms. For this reason, it was obtained from synthesis. The purity of dimethyltryptamine obtained after the synthetic reaction was >99% with regard to analysis (NMR ^{1}H, ^{13}C and HPLC–ESI-MS). The purity of DMBO was >99.9% in accordance with Sigma–Aldrich® report.

3.2. Synthesis of *N*,*N*-dimethyltryptamine

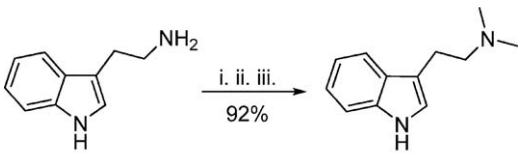
The synthesis of dimethyltryptamine was performed according to a modified procedure based on the selective dimethylation method (Giumanini et al., 1980), Scheme 1. Sodium borohydride (57 mg, 1.5 mmol) was slowly added to a stirred solution of tryptamine (160 mg, 1.0 mmol) in tetrahydrofuran at 0 °C. 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 alkalinized with NaOH pellets until reaching pH 14. 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 recrystallization with *n*-hexane/ethyl acetate (80:20). White crystals with a melting point of 64 °C were obtained. The structure was confirmed on the basis of the ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 2.70 (6H, s, N(C**H**$_3$)$_2$); 3.25 (2H, t, J = 7.22, C**H**$_2$CH$_2$N(CH$_3$)$_2$); 3.27 (2H, t, J = 6.80, CH$_2$C**H**$_2$N(CH$_3$)$_2$); 6.96 (1H, s, C=C–**H**); 7.2–7.5 (4H, m, Ph); and LC–ESI-MS (m/z) data: 189 [M+H]$^+$; 145 [M−N(CH$_3$)$_2$+H]$^+$; 117 [M−(CH$_2$)$_2$N(CH$_3$)$_2$+H]$^+$.

3.3. Preparation of standard solutions

Working solutions of DMT at a concentration of 1.0 mg/mL were prepared in chloroform with volumetric glassware. The internal standard solutions were prepared at a concentration of 1.0 mg/mL in hexane with volumetric glassware. Stock solutions were stored at 4 °C when it is not in use.

3.4. Instrumentation

Proton NMR experiments were carried out using Bruker® (Karls-ruhe, Germany) DPX 300 spectrometer operating at 300.13. The instrument was equipped with a multinuclear 5 mm probe



i. $NaBH_4$, THF, 0°C; ii. H_2SO_4, CH_2O, H_2O; iii. NaOH

Scheme 1. Synthesis of *N*,*N*-dimethyltryptamine.

operating in a temperature of 298 K. The chemical shifts were reported in ppm with tetramethylsilane (TMS) add in solvent ($CDCl_3$) as internal standard (0.0 ppm). The typical acquisition parameters optimized for qNMR experiments were as follows: single pulse with 30°, preacquisition delay of 5 μs, acquisition time 3.4 s, relaxation delay 10 s (in order to ensure that all protons were totally relaxed), window 10 ppm, 32 k data points after16 scans (AQ = 5.30 s), yielding a digital resolution of ~0.3 Hz. Data processing was performed offline with Top Spin (Bruker®, Karlsruhe, Germany, 2006) program package. Digital filter was used and each FID was multiplied by an exponential window function (lb 0.3 Hz) before Fourier transformation. Phase correction and base line were done manually using two expanded regions at both ends after performing a standard PH correction of the full spectrum. Automatic integration for selected signals was adopted throughout.

The DMT content of the solution was determined after integration of well separated signals of $N(C\mathbf{H}_3)$ at 2.70 ppm (singlet, 3*H*) and for 2,5-dimethoxybenzaldehyde $Ph(OC\mathbf{H}_3)_2$ at 3.80 and 3.89 ppm, (doublet, 6*H*). This choice was made taking into consideration some important aspects: its chemical shift, the absence or negligible (that does not affect the validation parameters) overlapping, and their intensity, that lead to lower limit of detection. The area ratios produced by protons of DMT and internal standard were used for quantification.

3.5. Plant material

P. viridis used in ayahuasca extract was collected by some specimens cultivated at the *Santo Antônio* farm in *Araçoiaba da Serra*, São Paulo state, Brazil (23°31′48″S 47°37′36″W). The species were identified by Dr. Sigrid Luiza Jung-Mendaçolli from the Agronomic Institute of Campinas (Department of Agriculture and Supply, Government of São Paulo) where exsiccates are deposited under the code 48679. The leaves were collected in January 2007, from the apical, intermediate and basal sections of a bush of 6.5 feet high, cultivated under solar radiation. The collected materials were blended to obtain a homogeneous sample.

3.6. Sample extraction

Initially, an aliquot of ayahuasca sample was centrifuged at 10,000 × *g* for 5 min to separate the solid phase of the tea from the aqueous phase. The latter was filtered by filter Millex® HV (PVDF) 0.45 μm and only after this process the sample went to the stage of extraction. During the extraction, the following solutions were added in a flask with 20 mL of capacity: 3 mL of the liquid phase of filtered tea, 0.5 mL of solution of sodium hydroxide 5N, 0.5 mg of solid NaCl, 500 μg DMBO and 5 mL of hexane. Then the mixture was shaken in an oscillating table for 20 min. The organic phase was separated and 0.5 g of anhydrous $MgSO_4$ was added. This suspension was filtrated and, subsequently, the solvent was evaporated under vacuum. The residue was reconstituted with 0.6 mL of deuterated chloroform ($CDCl_3$), placed in NMR 5 mm Norell XR-55 tubes (Norell, Landisville, NJ, USA) in order to be read in the NMR equipment.

3.7. Limit of detection (LOD) and lower limit of quantification (LLOQ)

LOD and LLOQ were determined by an empirical method, which consists of analyzing some series of samples containing decreasing amounts of the analyte. The LOD was the lowest concentration that presented a relative standard deviation (RSD) and did not exceed 20%. And the LLOQ was the lowest concentration which presented a RSD that did not exceed 10%.

3.8. Linearity

The study of linearity was performed by the analyses of water samples in triplicate submitted to the method spiked with the following concentrations for DMT: 25, 50, 100, 200, 500 and 1000 mg/L.

3.9. Recovery

The efficiency of the liquid–liquid extraction method was evaluated through the recovery studies that were performed by preparing two sets of samples of each concentration. One of them (set A), consisting of three concentrations of dimethyltryptamine (75, 300 and 750 mg/L) was extracted using the method described in Section 3.6 (processed). The analyses were performed in six replicates for each concentration. The other one (set B) also consisted on six replicates of each concentration (75, 300 and 750 mg/L). However, the extract was spiked with standard solutions of DMT before drying under nitrogen stream (unprocessed). To both sets (A and B), the internal standard was added prior to the extraction of the matrix. The absolute recovery was evaluated through the comparison of the mean response of extracted samples spiked before the extraction (processed) and the response of the extracted blank matrix to which analytes had been added at the same concentration just before the drying step (unprocessed). The unprocessed response represented 100% recovery.

3.10. Intra-assay precision

Precision defined as the relative standard deviation (RSD) was determined by intra-assay. They were carried-out by analyzing water samples spiked with DMT in the concentration of 75, 300 and 750 mg/L in six replicates.

3.11. Specificity

The specificity of the method was tested by analyzing eight samples of different ayahuasca preparations, which was obtained from a religious group settled in the city of Araçoiaba da Serra, São Paulo state, Brazil. The tea was prepared by the religious group, boiling the leaves of *Psychotria viridis* together with the stems of *Banisteriopsis caapi*. The chemical shifts of signals of dimethyltryptamine and dimethoxybenzaldehyde were selected taking into consideration the intensity of signals and to avoid the possibility of overlapping: **DMT** (δ ppm) 2.70 ($N(C\mathbf{H}_3)_2$), 3.25 ($C\mathbf{H}_2CH_2N(CH_3)_2$), 3.27 ($CH_2C\mathbf{H}_2N(CH_3)_2$), 6.80 (C=C–**H**), 7.2–7.5 (Ph); **DMBO** 3.80 ($C\mathbf{H}_3O$), 3.89 ($C\mathbf{H}_3O$), 7.1–7.3 (Ph), 10.4 (CO**H**).

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