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Chemical Composition of Traditional and Analog Ayahuasca

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ABSTRACT

Traditional ayahuasca can be defined as a brew made from Amazonian vine *Banisteriopsis caapi* and Amazonian admixture plants. Ayahuasca is used by indigenous groups in Amazonia, as a sacrament in syncretic Brazilian religions, and in healing and spiritual ceremonies internationally. The study aimed to determine concentrations of the main bio- and psychoactive components of ayahuasca used in different locations and traditions. We collected 102 samples of brews from ayahuasca-using communities. Concentrations of *N,N*-dimethyltryptamine (DMT), tetrahydroharmine, harmine, and harmaline were determined by ultra-high performance liquid chromatography coupled to tandem mass spectrometry (UHPLC-MS/MS). Qualitative analyses for non-traditional additives (moclobemide, psilocin, yuremamine) were performed by high resolution mass spectrometry. Higher and more variable concentrations of DMT in neoshamanic ayahuasca samples compared to indigenous samples may indicate use of higher and more variable proportions of DMT-containing admixture plants. From European samples, we found two related samples of analog ayahuasca containing moclobemide, psilocin, DMT, yuremamine, and very low concentrations of *B. caapi* alkaloids. Some analogs of ayahuasca (*Peganum harmala, Mimosa tenuiflora*) were used in Europe. No analogs were found from Brazil or Santo Daime ceremonies in Europe. We recommend awareness about the constituents of the brew and ethical self-regulation among practitioners of ayahuasca ceremonies.

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KEYWORDS
Ayahuasca; Daime; DMT; harmaline; harmine; tetrahydroharmine

Introduction

Ayahuasca is a traditional concoction made from Amazonian vine *Banisteriopsis caapi*, which contains β-carboline alkaloids harmine (HME), harmaline (HML), and tetrahydroharmine (THH). Interaction of *B. caapi* alkaloids with admixture plants (traditionally *Psychotria viridis* or *Diplopterys cabrerana*) containing psychedelic *N,N*-dimethyltryptamine (DMT) gives ayahuasca psychoactive properties (Barbosa et al. 2016).

DMT binds to 5-HT_{1A}, 5-$HT_{2A,}$ 5-HT_{2C} (Keiser et al. 2009), σ_1 (Fontanilla et al. 2009) and trace amine (Jacob and Presti 2005) receptors. HME and HML are reversible inhibitors of monoamine oxidase type A (MAO-A). DMT alone is not psychoactive after oral administration, but in the case of ayahuasca, reversible inhibition of peripheral MAO-A by the β-carbolines allows DMT to reach the central nervous system (Santos et al. 2016a). Sometimes other plants are added to the brew to modify or potentiate its effect. Some admixtures can be toxic and/or increase the risk of inducing psychoses (Ray and Lassiter 2016).

Since there are many different ayahuasca formulations, we operationally define as "traditional ayahuasca" the brew that is made from *B. caapi* and traditional DMT-containing Amazon species *Psychotria viridis* and *Diplopterys cabrerana*. Traditional ayahuasca may or may not include other Amazonian plant admixtures.

Different varieties of *B. caapi* exist. Botanical varieties *caupuri* (with knotty stems) and *tucunaca* (with smooth stems) are reported to differ in their effects (Callaway, Brito, and Neves 2005). Another classification of varieties of the ayahuasca vine by "colors" (e.g., red, black, *cielo, ourinhos*), based on traditions from Peru and Brazil, is used at psychonaut forums and online vendors. Indigenous people who traditionally use ayahuasca have their own classifications of varieties of the vine.

Indigenous people of Amazonian rainforests use ayahuasca for healing and divination. Brazilian syncretistic religions *Santo Daime, União do Vegetal* and *Barquinha* use ayahuasca as their sacrament (Carlini 2003).

Group rituals with the use of ayahuasca have become a new form of psycho-spiritual practice. Ayahuasca ceremonies and retreats have developed into a small but distinctive branch of the tourism industry in South America (McKenna 2004), with benefits and risks to involved cultures. Marlene Dobkin de Rios, after

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The supplemental data for this article can be accessed here.

researching ayahuasca use in Peru, cautioned against endangering of unsuspecting tourists by untrained "neo-shamans" who are "prone to use local witchcraft plants (read *poisons*) to ensure that their clients have a good trip" (Dobkin de Rios and Rumrrill 2008, 72).

Healing and spiritual ceremonies with ayahuasca have spread from Amazonia into North America and Europe (Labate and Jungaberle 2011).

Analogues of ayahuasca ("anahuasca" or "pharmahuasca" (Ott 1999)) consisting of plant-derived or synthetic MAO inhibitors and a source of DMT (e.g. plants of genera *Mimosa, Acacia* or *Phalaris*) are sometimes used in ceremonies outside of South America and for psychonautic experimentation (Ott 1994). Ayahuasca analogues offer an alternative to commercialization of traditional ayahuasca. However, "anahuasca" and "pharmahuasca" are variable combinations of plants and chemicals with risks of toxicity (Ott 1996) and short history of human use. Risks increase if such substances are ingested without adequate knowledge of the composition and dose.

Acute effects of ayahuasca begin usually 15–30 min after ingestion, reach maximum intensity around 90 min, and last 2–6 hours depending on the dose. During ceremonies, ayahuasca is often ingested repeatedly. Among the reported effects are changes in perception (especially in vision), thinking and feeling, intensification of emotions, tendency to introspection, and closed-eyes visualizations (Anderson et al. 2012). Visions of diverse phenomenology may appear (Shanon 2002). Anxiety, nausea, vomiting, or diarrhea may occur (Gable 2007). Ritual users often consider vomiting and other forms of excretion as useful for healing and cleansing (Anderson et al. 2012).

Ayahuasca can be safely administered in controlled settings and several studies suggest that it has anxiolytic, antidepressant, and anti-addictive effects (Palhano-Fontes et al. 2019; Santos et al. 2016b). Long-term regular ritual ayahuasca use is reasonably safe (Bouso et al. 2012).

Being a plant preparation, traditional ayahuasca is variable in appearance, taste, and effects. Large variations in alkaloid profiles of ayahuasca samples from different sources (Callaway 2005a) and individual variations of metabolism of ayahuasca (Callaway 2005b) have been found.

Variability of the brew and individual variability of effects together make it difficult for users to assess the quality of the brew that they drink during the ceremony. Commercialization of ayahuasca rituals and illegal or unregulated status of ayahuasca in several countries create an incentive for providers of ceremonies to use substitutes instead of traditional ayahuasca. When compared to traditional ayahuasca, such preparations may be pharmacologically dangerous or reasonably safe. Nevertheless, serving ayahuasca substitutes to participants without their knowledge and consent may be considered unethical.

Therefore, our study aimed to determine and compare concentrations of main known bio- and psychoactive components of ayahuasca used in different locations (Europe and Brazil) and traditions (indigenous "shamanic", religious 'Santo Daime' and various 'neoshamanic' facilitators). Such knowledge enhances the safety of ceremonial use of ayahuasca by increasing awareness of users, communities, and professionals about the quality of ceremonially used herbal preparations.

Methods

Samples

One hundred and two samples (1–6 mL each) of ceremonially used psychoactive brews (Figure 1) were collected from ayahuasca ceremonies held in a variety of locations and traditions. Information about plant constituents of the sampled brew, its preparation, use, and effects was collected from providers of the samples. The countries where those ceremonies were held included Brazil, Netherlands, Estonia, Italy, Finland, Czech Republic, Greece, Portugal, Spain, and the USA.

The samples were labeled according to the context of use. For religious groups, the sample was labeled with the group's specification of the sacrament: "Daime" for Santo Daime (adding the type or "degree" of Daime

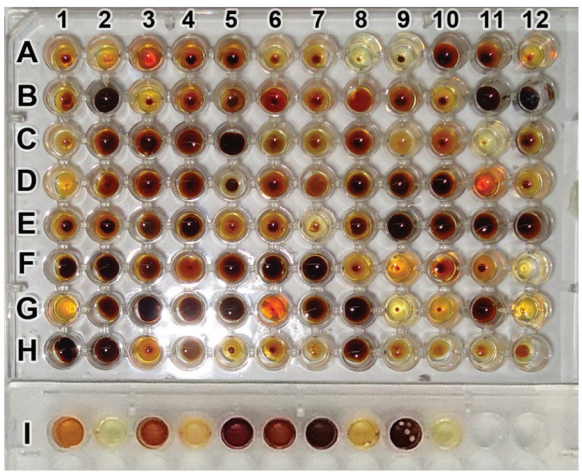

Figure 1. Samples of ayahuasca studied in this work (subsamples of 36 µL each). Concentrations of analytes (DMT, THH, HME, HML) and qualitative findings for additives are presented in Table 1. The darker dots in the centers of the conical wells in rows A-H are due to natural sedimentation over 48 h.

Table 1. Concentrations of analytes: arithmetic mean (mg/L) of three measurements, relative standard deviation (RSD, also called coefficient of variation, as percentage from the mean), and additives found in samples of ayahuasca. Locations of collecting the samples: Eur: Europe, Br: Brazil, US: USA. Analytes: DMT: *N,N*-dimethyltryptamine; THH: tetrahydroharmine; HME: harmine; HML: harmaline. Additives: H: *Peganum harmala*, M: moclobemide, P: psilocin, Y: yuremamine. "-" stands for images not available and for concentrations too low to detect with reasonable accuracy by the used procedure. Samples 39A and 39B were from the same facilitator and may represent the same batch of ayahuasca. For MS spectra for moclobemide and yuremamine, see Supplemental Information.

				DMT		THH		HME		HML		Additives
Sample	Collected	Characteristics	Figure 2	Mean	RSD%	Mean	RSD%	Mean	RSD%	Mean	RSD%	
1	Eur Feb 15	Mix shamanic+ neoshamanic	A1	751.7	2.1	390.0	2.2	646.7	2.9	27.5	3.2	
2	Eur Feb 15	Neoshamanic	A2	88.3	3.6	90.0	8.4	555.3	1.8	6.9	5.2	
4	Eur Feb 15	Daime	A3	888.3	3.1	1433.3	4.9	2141.7	4.4	80.0	6.3	
5	Eur Apr 15	Neoshamanic	A4	290.0	6.1	288.0	10.3	901.0	9.6	26.9	5.4	
6	Eur Apr 15	Neoshamanic	A5	669.3	1.9	1274.7	1.5	1725.3	2.3	66.7	3.5	
7	Eur Jun 15	Neoshamanic	A6	600.0	6.7	497.3	4.4	2146.7	9.1	53.3	11.5	
8	Eur Sep 15	Daime	A7	936.7	2.2	948.3	3.2	863.3	3.7	48.1	2.8	
9	Eur Nov 15	Neoshamanic	A8	411.7	1.9	388.3	7.1	391.7	4.5	240.0	3.6	H, Y
10	Eur Nov 16	*P. harmala* tea for pre-dose	A9	4.6	8.3	15.3	7.4	64.9	7.4	101.6	5.4	H
11	Eur Nov 16	Neoshamanic	A10	618.3	2	503.3	3.2	1430.0	3	16.5	12.5	
12	Eur Nov 16	shamanic	A11	653.3	3.7	570.7	6.9	1288.0	5.4	274.7	6.7	H?
13	Eur May 16	Neoshamanic	A12	1530.7	4.3	501.3	8.8	1277.3	3.6	40.9	1.3	Y
14	Eur Jul 17	Daime 3x1	B1	1493.3	3.9	2626.7	3.2	2421.3	3.9	173.3	2.7	
15	Eur May 17	Neoshamanic	B2	1314.7	2.3	-	-	-	-	-	-	M, P, Y
16	Br Mar 17	Daime	B3	776.7	1.6	1705.0	2.6	2315.0	3.1	143.3	2	
17	Eur Jan 17	Neoshamanic	B4	1608.0	2.8	805.3	2.3	2440.0	2.6	77.3	11.9	
18	Eur Jan 17	Daime	B5	193.3	6.7	305.3	11.1	746.7	7.1	17.3	13.3	
19	Eur Aug 16	Neoshamanic	B6	1454.7	3.2	870.7	4.7	2094.7	4.2	72.0	5.6	
20	Br Oct 16	Shamanic	B7	652.0	12.9	1266.7	13.5	342.0	4.3	25.7	4.6	
21	Eur Sep 16	Daime	B8	906.7	4.9	2986.7	4.3	3080.0	4.9	173.3	7.1	
22	Eur Jul 17	Daime from *gel*	B9	608.0	7.5	642.7	7.8	712.0	12.2	29.5	1.1	
23	Eur Oct 15	Neoshamanic	B10	668.0	11.5	1324.0	13.7	2000.0	12.2	148.0	14.3	
24	Eur Aug 15	Neoshamanic	B11	1293.3	2.5	610.7	3.3	1085.3	0.9	-	-	
25	Eur May 17	Neoshamanic	B12	1840.0	2.9	66	-	100	-	0.2	-	M, P, Y
26	Eur Jul 16	Daime	C1	573.3	3.4	736.0	4.1	944.0	6.2	49.3	4.7	
27	Eur Aug 16	Daime	C2	366.7	1.3	313.3	4.5	400.0	6.1	12.1	22.8	
28	Eur May 17	Neoshamanic	C3	1128.0	2.1	930.7	2.8	1421.3	2.7	-	-	
29	US Apr 17	Daime *mel*	C4	1344.0	0.6	3874.7	2.2	4440.0	1.1	386.7	2.4	
30	Eur Jun 17	Daime	C5	1698.7	2.7	1192.0	1.8	1957.3	2.3	40.0	0	
31	Br Jul 17	Shamanic	C6	628.0	3.4	1076.0	3.4	717.3	4.2	49.3	4.7	
32	Br Jul 17	Neoshamanic	C7	810.7	3	2256.0	3.1	4032.0	2.3	173.3	2.7	
33	Br Jul 17	Daime 1º *grau*	C8	456.0	3	1334.7	2.7	966.7	4.8	94.7	4.9	
34	Br Jul 17	Daime 5x1	C10	1538.7	2.2	3861.3	3.5	3386.7	3.7	354.7	4.7	
35	Br Jul 17	Daime 1º *grau apurado*	C11	592.0	4.2	1182.7	5.8	820.0	6.8	80.0	10	
36	Br Jul 17	Daime 2x1	C12	757.3	1.5	1665.3	1.1	1354.7	1.7	68.0	0	
37	Br Aug 17	Neoshamanic	D1	726.7	4.1	1830.7	3.9	1782.7	4.8	181.3	5.1	
38	Br Aug 17	Neoshamanic	D2	702.7	2.8	1240.0	3.5	1370.7	3.5	57.3	4	
39 A	Br Aug 17	Neoshamanic	D3	948.3	4.1	1360.0	6.1	2031.7	5.2	61.7	4.7	
39 B	Br Aug 17	Neoshamanic	D4	955.0	6.7	1385.0	6.3	2080.0	7.3	68.3	11.2	
40	Eur Aug 16	Neoshamanic	D5	340.4	2.9	121.3	6.2	140.7	9.2	6.7	5.3	
41	Eur Sep 17	Daime from *gel*	D6	515.6	14.9	326.7	14.7	1864.4	13.1	40.7	6.2	
42	Eur Sep 17	Daime	D7	408.0	15.2	400.0	18.5	370.7	20.8	34.0	36.7	
43	Eur Aug 17	Daime from *gel*	D8	417.8	33.3	305.3	30.6	281.8	46.6	10.1*	34.6*	
44	Eur Sep 17	Daime	D9	277.3	6.7	193.3	6.7	393.3	8.6	23.2	1.2	
45	Eur Sep 17	Neoshamanic	D10	1725.0	3.2	174.0	3.0	975.7	13.3	20.0	0.0	
46	Eur Nov 17	Neoshamanic	D11	1396.7	3.4	2156.7	5.9	1742.4	10.2	103.6	4.8	
48	Eur Dec 16	Daime	D12	735.6	1.9	1380.0	1.7	1037.8	1.3	120.0	0.0	
49	Eur Oct 17	Neoshamanic	E1	972.0	14.5	864.4	12.7	965.0	14.8	28.3*	1.0*	
50	Eur Oct 17	Daime "todos os graus" (all degrees)	E2	408.9	4.1	404.4	2.5	955.6	5.2	25.0	2.0	
51	Eur Jun 16	Daime	E3	275.8	6.1	208.1	5.9	439.4	8.0	19.8	3.9	
52	Eur Sep 16	Shamanic	E4	691.1	9.5	1197.8	10.1	1040.0	7.9	52.0	0.0	
53	Eur Mar 17	Daime	E5	655.6	6.0	846.7	4.4	768.9	4.1	53.7	2.8	
54	Eur Nov 17	Daime 4x1	E6	855.6	5.6	1615.6	5.4	2002.2	5.0	146.7	4.5	
55	Eur Nov 17	Umbandaime**	E7	493.3	0.6	335.0	3.0	726.7	4.5	45.2	6.8	
56	Eur Nov 17	Umbandaime**	E8	1090.7	5.9	752.3	10.9	508.0	7.1	39.3	2.9	
57	Eur Dec 17	Daime from *gel*	E9	546.7	4.7	198.3	3.9	1395.0	2.2	18.0	0.0	
58	Eur Dec 17	Neoshamanic	E10	329.2	13.4	231.3	8.8	416.7	11.1	12.2	2.4	
59	Eur Dec 17	Daime from *gel*	E11	458.7	1.3	371.7	2.8	586.7	3.2	18.3	5.7	
60	Eur Dec 17	Shamanic	E12	588.9	5.8	840.0	5.2	1133.3	5.3	88.9	8.7	
61	Eur Nov 17	Shamanic	F1	793.3	2.9	1031.1	2.6	1586.7	1.8	113.3	0.0	
62	Eur Jan 18	Shamanic	F2	513.3	2.2	448.9	2.3	1426.7	1.2	45.3	5.5	
63	Eur Jan 18	Shamanic	F3	215.6	7.1	289.3	2.6	540.0	8.1	70.0	5.5	
64	Eur Feb 18	Neoshamanic	F4	575.6	7.1	1926.7	4.2	1577.8	5.1	117.8	8.6	

(*Continued*)

Table 1. (Continued).

				DMT		THH		HME		HML		Additives
Sample	Collected	Characteristics	Figure 2	Mean	RSD%	Mean	RSD%	Mean	RSD%	Mean	RSD%	
65	Eur Mar 18	Daime from *gel*	-	382.8	4.8	283.8	1.6	521.2	4.1	4.0*	43.3*	
66	Eur Apr 18	Neoshamanic	F5	633.3	2.0	848.3	2.8	1406.7	3.6	43.0	2.9	
67	Eur May 18	Daime	F6	1050.7	2.7	2712.0	3.1	2749.3	5.1	330.7	6.1	
68	Eur May 18	Daime	F7	862.2	2.9	1922.2	3.1	1773.3	3.7	208.9	3.7	
69	Eur Jun 18	Daime from *gel*	F8	500.0	1.0	766.7	3.2	1310.0	5.8	78.3	7.4	
70	Eur Jun 18	Neoshamanic	F9	1026.7	23.4	629.3	19.1	694.0	11.9	42.0	6.7	
71	Eur Jun 18	Neoshamanic	F10	1729.2	5.1	407.3	8.7	558.7	5.4	20.2	5.7	
72	Eur Jun 18	Shamanic	F11	537.0	12.6	416.0	9.4	1484.0	20.9	66.3	11.3	
73	Eur Jun 18	Daime	-	471.1	5.4	895.6	11.7	2231.1	6.7	148.9	5.2	
74	Eur Nov 17	Daime *1º grau apurado*	F12	506.7	8.3	968.3	7.8	718.3	7.5	81.7	3.5	
75	Eur Jan 18	Daime 3 × 1 supernatant	G1	829.3	13.7	1378.0	12.3	1181.3	14.8	99.3	9.0	
76	Eur Jan 18	Daime 4 × 1 from *gel*	G2	848.9	0.5	1122.2	2.8	1235.6	8.2	84.4	4.6	
77	Eur Dec 17	Daime *mel*	G3	1396.7	1.5	1012.2	4.2	2091.7	6.2	90.0	9.6	
78	Eur May 17	Neoshamanic	G4	628.9	1.6	537.8	5.2	977.8	6.5	6.7*	-*	
79	Eur Jan 18	Daime 3 × 1 sediment	G5	1380.0	5.5	2338.0	5.4	2205.0	5.9	196.1	5.9	
80	Eur May 18	Neoshamanic	G6	1200.0	3.8	32.0*	12.5*	1039.4	8.7	-	-	
81	Eur Jun 18	Daime from *gel*	G7	341.4	5.7	217.2	8.4	407.1	10.1	9.3	3.1	
82	Eur Sep 17	Daime	G8	986.7	0.0	1031.1	3.1	1646.7	3.2	71.1	5.4	
83	Eur Jan 18	Daime mixed	-	148.7	6.6	121.3	15.0	442.7	12.6	7.3	7.9	
84	Eur Mar 17	Daime	-	152.7	2.7	90.0	6.7	269.3	5.8	-	-	
85	Br Jun 18	Daime 1º *grau*	G9	430.0	2.0	593.3	2.6	918.3	3.7	60.7	1.0	
86	Br Jun 18	Daime 3 × 1 with mold	G10	640.0	2.8	1106.7	2.8	1202.2	4.4	128.9	3.0	
87	Br Jun 18	Daime *mel*	G11	1780.0*	5.6*	2716.7	3.3	2793.3	1.7	300.0	5.8	
88	Br Jul 18	Neoshamanic	G12	633.3	3.0	921.7	3.0	588.3	2.1	66.7	4.3	
89	Br Jul 18	Daime *estrela*	H1	1226.7	7.3	1140.0	10.7	2376.7	9.9	66.7*	31.2*	
90	Br Jul 18	Neoshamanic	H2	1433.3	7.6	1650.0	6.6	4416.7	5.7	220.8	8.6	
91	Eur Sep 17	Neoshamanic	I1	1160.0	5.4	743.3	10.3	873.3	11.5	19.2	5.4	
92	Eur Sep 17	Shamanic	H3	748.9	8.0	1120.0	4.7	1891.1	5.4	157.8	2.4	
93	Br Jul 18	Neoshamanic	I2	213.3	10.3	528.0	13.3	817.3	13.9	42.0	6.7	
94	Br Jul 18	Daime 1º *grau*, fermented	H4	357.3	5.6	1078.7	5.2	1161.3	6.0	118.7	8.5	
95	Br Jul 18	Daime 1º *grau*, fermented and boiled	H5	429.3	5.7	1326.0	2.3	1560.0	6.6	156.0	13.3	
96	Br Jul 18	Daime 2x1	H6	451.1	2.3	1346.7	3.0	1762.2	4.8	166.7	4.0	
97	Br Aug 18	Daime 1º *grau*	H7	488.0	7.0	708.0	16.9	356.0	9.6	34.0*	8.3*	
98	Br Aug 18	Daime *mel*	H8	2686.7*	4.1*	2436.7	6.6	1420.0	5.3	156.7	3.7	
99	Br Aug 18	Daime 1º *grau*	H9	334.7	4.8	474.7	3.5	324.0	3.3	44.0	10.5	
100	Br Aug 18	Daime 2º *grau*	H10	277.3	6.8	416.0	4.4	278.7	6.0	24.0*	16.7*	
101	Br Aug 18	Daime 2º *grau* concentrated	H11	415.6	2.5	395.6	5.4	284.4*	2.7*	13.3*	-*	
102	Br Aug 18	Daime 2º *grau apurado*	H12	584.4	2.4	728.9	6.0	431.1	4.5	33.3*	-*	
103	Br Aug 18	Hoasca UDV	-	138.0	9.0	454.0	4.3	866.0	3.1	50.0	4.6	

* The concentration is of diminished reliability due to its measured value being out of the linear range of the calibration curve.
** Umbandaime is a syncretic religious movement with influences from Daime and Afro-Brazilian mediumship.

according to the tradition if known) and "Hoasca" for the only sample received from União do Vegetal.

The sample was labeled "shamanic" if the leader of the ceremony from where the sample was collected came from a South American indigenous community with traditional ayahuasca use.

A broad label "neoshamanic" was assigned to the remaining samples from facilitators of mainly "modern western" enculturation, spanning various levels of indigenous influence, competence, and responsible attitude to their practice. Differently from Dobkin de Rios (Dobkin de Rios and Rumrrill 2008), we use the term "neoshamanic" without any value judgment, in line with the use of the term 'neoshamanism' in anthropological research literature (DuBois 2011).

H. Kaasik as a member of Santo Daime Church knows about ritual preparation (*feitio*) and use of Daime (ayahuasca in this religious context) due to her experience in two Brazilian Santo Daime communities: a rural Santo Daime church (state of Pará, site 1) visited repeatedly during years 2016–2019 and another Santo Daime community (state of Rio de Janeiro, site 2) visited

in 2018. Some of the information about ceremonial ayahuasca use in Europe was collected during a previous study (Kaasik and Kreegipuu 2020).

Mass spectrometry analyses

Samples were sent for quantitative analysis to the Institute of Chemistry of the University of Campinas, SP, Brazil. Concentrations of DMT and characteristic alkaloids from *B. caapi* (tetrahydroharmine, harmine, and harmaline) in the samples were determined by UHPLC-MS/MS using a previously validated method (Souza et al. 2019). Analyses were conducted using a mass spectrometer Quattro Micro API series (Waters Corp., Milford, MA, USA) with electrospray ionization (ESI) operated in the positive ion mode and a triple quadrupole mass analyzer. An UHPLC system equipped with a Waters ethylene-bridge hybrid (BEH) C18 column (50 × 2.1 mm, 1.7 µm) using gradient elution with a mobile phase composed of water and methanol was applied for separation of the analytes. A calibration curve for the four standards was prepared from hydromethanolic working solutions of standards. Diphenhydramine hydrochloride was used as internal standard. Samples and standards were analyzed using a 1 µL injection volume. MS/MS analysis was performed using selected reaction monitoring (SRM) of the protonated molecular ions for the analytes and internal standard.

Qualitative analyses for expected non-traditional additives such as moclobemide, yuremamine, and psilocin in samples 1 – 39B were performed by high resolution mass spectrometry using a Waters Xevo QTOF (Manchester, UK) mass spectrometer. The identity of the compounds was determined based on their accurate masses and fragmentation patterns compared to reference mass spectra, since direct infusion high resolution tandem mass spectrometry experiments were performed. However, the analysis of reference standards was not executed, which is an experimental limitation.

Samples analyzed in this work are preserved at the Institute of Chemistry of University of Campinas, Brazil. This work was registered at the Brazilian National System for the Management of Genetic Heritage and Associated Traditional Knowledge – SisGen (protocol A6E33A0).

Results

Plant constituents and preparation of ayahuasca

Organizers of ceremonies named Brazil, Peru, and Hawaii as locations of preparation of their plant medicines. In the Brazilian religious traditions, ayahuasca is usually prepared from fresh stems of *B. caapi* and fresh leaves of *P. viridis*. In Europe, ayahuasca is usually imported from South America in liquid form, or sometimes prepared from imported dried plants or concentrates.

Brazilian Daime: preparation and use

Preparation of ayahuasca used as a sacrament in Santo Daime religion is an organized community ritual, *feitio*, lasting several days. Like the religion itself, the sacrament is also called Daime, meaning "give me" in Portuguese.

Daime was prepared from fresh stems of *B. caapi* and fresh leaves of *P. viridis* in mass proportion 5:1 and water by boiling over fire. No other plants or substances were added to the brew. Interestingly, the bark of *B. caapi* was discarded despite containing active compounds (Wang et al. 2010).

Although using only two plant species, several different types or "grades" (*graus*) of the sacrament are produced during the *feitio* (Table 1). Differences between them result from different preparation procedures. First grade (*primeiro grau*) Daime is made by filling the brewing pot with layers of fresh plants and water, boiling for approximately an hour, using the resulting liquid (*cozimento*) for filling another pot with fresh plants and boiling it once more. This is considered the most traditional type of Daime. More concentrated types of sacrament (e.g., "*dois por um*" = 2 × 1, "*três por um*" = 3 × 1, 5 × 1, "*mel*") are made by combining several (respectively 2, 3, 5 or more) subsequent brews of the already used plants, and concentrating the liquid by additional boiling. *Gel* is an almost solid concentrate of *Daime*, produced mostly for efficient transportation. *Gel* is diluted with water (ca 1:5) before use.

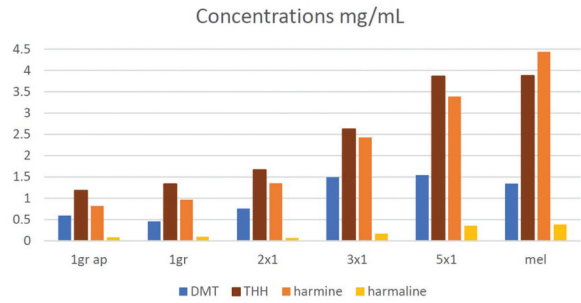

Figure 2. Concentrations of *N,N*-dimethyltryptamine (DMT), tetrahydroharmine (THH), harmine and harmaline in different "degrees" of Daime. Abbreviations: 1gr ap =*primeiro grau apurado*, 1gr =*primeiro grau*. Data from samples collected before August 2017, from left to right: 35, 33, 36, 14, 34 (all prepared in the site 1) and 29 (reportedly prepared in Hawaii).

Daime of *primeiro grau* or *segundo grau* is enhanced, respectively, to *primeiro grau apurado* or *segundo grau apurado* by boiling it once more with the addition of leaves of *P. viridis*.

Different grades of Daime differ in overall concentration or "strength", those differences are considered when determining dosages. The usual ceremonial dosage of *primeiro grau* (samples 33 and 94) or Daime 2 × 1 (samples 36 and 96) for women was around 25 mL, for men somewhat larger. Higher grades of Daime and especially *mel* are considered stronger and are used in smaller dosages, e.g., ca 12 mL of Daime 3 × 1 (sample 14) or one tablespoon of *mel* (sample 29). Some ceremonies are deliberately more intense; for example, a session with 50 mL of Daime *mel* (sample 98) per participant was reported from a Brazilian community. The overall increasing concentration of active constituents corresponds well with the increasing grade of Daime (Figure 2).

Different grades of Daime differ also in relative concentrations of the active principles (see Figure 2 and Table 1) despite having been made from the same plants. Ratios of concentrations of DMT and THH to harmine in brews tended to decrease with the increase of the grade of the Daime from *primeiro grau* to 2 × 1, 3 × 1, 5 × 1 and *mel*. Grades of Daime also differ in taste and in appearance (as seen in Figure 1).

Grades of Daime differ also in their subjective effects. When describing the difference, it is said that first grade (*primeiro grau*) Daime 'has more light' than other grades, meaning that its effect was subjectively different from other grades of Daime. Its effect seems also to be more easily controlled and experienced users often prefer it to the other grades.

Use of analog plants in neoshamanism

The use of DMT-containing plants other than *P. viridis* or *D. cabrerana*, or other MAOI-containing plants instead or in addition to *B. caapi* (the so-called analog plants) was investigated. Use of non-traditional (analog) ingredients of ayahuasca (*Peganum harmala* and/or *Mimosa tenuiflora*) with partially informed consent of the participants by five different facilitators was recorded in Europe.

Some facilitators in Europe used *jurema* (*Mimosa tenuiflora*) as a source of DMT instead of traditional *P. viridis*. Participants were informed about this substitution on request or occasionally but not regularly/proactively. An experienced participant commented this as: "It is not important where the DMT comes from, the magic is in the vine."

Two facilitators of ceremonies in Europe used to give *Peganum harmala* "tea" (sample 10) to participants of the ceremony approximately half an hour before ayahuasca. Participants were told what it was and that it was needed "to prepare the body for ayahuasca."

Neoshamanic ceremonies are usually not explicitly announced as ayahuasca ceremonies but are called "circles" or "retreats" by the organizers. The drink is called "the medicine" or other indirect terms. Organizers encourage also participants to use indirect expressions instead of explicitly asking about ayahuasca and its constituents over e-mail, social media or phone. Such precautions are used for protection of the practice in countries where the legal status of ayahuasca is unclear, but they may also be used to conceal the use of substitutes.

Chemical analyses

Substantial and variable concentrations of DMT were detected in all samples that were used as ayahuasca. Concentrations of DMT, THH, harmine, and harmaline in 102 samples are presented in Table 1.

Samples excluded from summary data processing

Sample 10 was presented to participants not as ayahuasca but as *P. harmala* tea, ingested before drinking ayahuasca to "prepare the body for ayahuasca". Samples 15 and 25 did not contain substantial concentrations of *B. caapi* alkaloids, so they were actually not ayahuasca (see Table 1). Therefore, samples 10, 15, and 25 were excluded from the summary data processing.

Composition of ayahuasca used in different contexts

All samples from Brazil and most samples from Europe contained substantial but variable concentrations of DMT, THH, and harmine. The same applied to all samples of Daime, used either in Brazil or Europe. User-reported strengths and dosages of different grades of Santo Daime corresponded quite well to concentrations of the analytes, as shown in Figure 2.

Average (minimal – maximal) concentrations (mg/L) of the analytes in 99 samples of ayahuasca were: DMT 764 (88–2687); THH 995 (32–3875); harmine 1318 (-141–4440); harmaline 85 (4–387).

Ratios of concentrations of the alkaloids also presented a large range. Average (minimal – maximal) percentages from the sum of the concentrations of the 4 analytes were: DMT 26.2% (9.2–63.7%); THH 29.8% (1.4–55.4%); harmine 41.5% (15.0–75.0%); harmaline 2.5% (0.3–16.8%).

Average ratio of concentrations of harmaline over harmine was 0.0668 ± 0.0667 (0.0069–0.6127). Some facilitators may add *P. harmala* directly to the ayahuasca. We propose that these manifests in chemical analyses as an elevated ratio of the concentration of harmaline over harmine, as seen in samples 9 (0.6127)

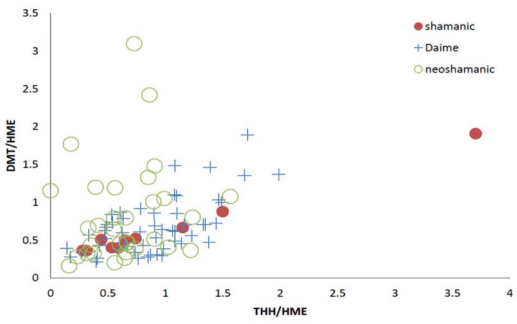

Figure 3. Ratios of concentrations of DMT and THH to the concentration of harmine in different samples of ayahuasca from shamanic, Daime and neoshamanic ceremonies. The ratios are based on the data in Table 1. Samples 15 and 25 are far outside of the graph area due to very low concentration of harmine.

and 12 (0.2133). Both facilitators who offered these brews have used *P. harmala* in their ayahuasca ceremonies. Harmaline/harmine concentration ratios around 0.1 have been detected in brews from Santo Daime where *P. harmala* is not used.

Comparing shamanic (n = 10) and neoshamanic (n = 32) brews, the average concentration of DMT in neoshamanic samples (891 ± 460 mg/L) exceeded that in shamanic samples (602 ± 161 mg/L). The variance of concentration of DMT was higher in neoshamanic samples due to scattering toward higher DMT concentrations (Figure 3). As seen in Figure 3, there was also a trend toward higher DMT/HME ratios among Daime samples (n = 53) compared to shamanic samples.

Samples obtained from indigenous shamans showed significant positive correlations between concentrations of DMT and THH (r = 0.756, p = .011) and between concentration ratios of DMT/HME and THH/HME (r = 0.994, p < .001). These correlations were also significant among Daime samples: between DMT and THH, r = 0.730, p < .001, and between DMT/HME and THH/HME r = 0.620, p < .001. Among neoshamanic samples these correlations were not significant (between DMT and THH r = 0.127, p = .490, between DMT/HME and THH/HME r = 0.137, p = .456).

Use of additives and substituents

Moclobemide (a pharmaceutical MAOI antidepressant) and psilocin (a psychedelic compound contained in mushrooms of the genus *Psilocybe*) were qualitatively confirmed by chemical analyses in samples 15 and 25. These samples did not contain substantial concentrations of *B. caapi* alkaloids but had high concentrations of DMT (see Table 1). These samples were taken from ceremonies held in Europe by the same facilitator during two consecutive nights. The decoction was psychoactive at doses in the range 25–50 mL, but also caused a lot of vomiting and especially diarrhea. According to the organizer of the ceremonies, this brew contained *Mimosa* as the source of DMT, this was confirmed by detection of yuremamine.

The facilitator who concocted the brew was contacted and asked to confirm and explain the addition of moclobemide. The facilitator confirmed adding moclobemide and explained that they got some bad vine from the internet and wanted to make sure that all participants would have an experience. The facilitator also said that adding moclobemide was safer than adding *P. harmala* and denied adding *Psilocybe* mushrooms or psilocin to the brew.

Discussion

The majority of the psychoactive brews analyzed in this study were found to be chemically consistent with traditional ayahuasca.

Concentrations of analytes were variable (as expected of a natural product) but mostly in a range detected in samples of ayahuasca (Callaway 2005a; Gaujac et al. 2012; Souza et al. 2019). They followed previously observed ordering of concentration of the alkaloids HME ~ THH > DMT > HML (Souza et al. 2019). However, considerably higher concentrations were found in ayahuasca prepared by an unspecified Brazilian religious group (Santos, Navickiene, and Gaujac 2017).

High HML/HME ratios in literature: errors or additives?

Unusually high harmaline concentrations and harmaline/harmine ratios were detected in samples 9 and 12. This may indicate presence of harmaline-containing additives, probably *P. harmala*. However, much higher harmaline/harmine ratios in ayahuasca have been reported in previous studies and causes of those findings have not been sufficiently discussed.

Potencies of harmine and harmaline as MAO-A inhibitors are different (Santillo et al. 2014). They also found nonlinear (antagonistic) interaction between harmine and harmaline at 50% MAO-A inhibition. The antagonism increased with decreasing levels of MAO-A inhibition, therefore, it may be even stronger at lower levels of MAO-A inhibition which correspond to lower doses of ayahuasca. Also, these compounds differ in other biochemical properties beyond MAO inhibition. These differences in biochemical properties of harmaline and harmine may cause differences in subjective and pharmacological effects of ayahuasca brews with different

proportions of concentrations of these compounds. The differences of the subjective effects of brews containing *P. harmala* and *B. caapi* have been described, based on experiences shared in online forums: "*substituting, say, Syrian rue for the ayahuasca vine, even though the rue contains the same harmala alkaloids, does apparently make an experiential difference. The experience with rue has been described as crystalline, cold, overwhelming, erratic, and uncaring, compared with that of the ayahuasca vine, which has been described as warm, organic, friendly, and purposeful.*" (Beyer 2009, 253).

A very high concentration of harmaline and a very high harmaline/harmine ratio in an ayahuasca sample from Netherlands was recently reported (Uthaug et al. 2018): a 200-mL portion of their sample "Netherlands 1" contained 371.6 mg of DMT, 485.5 mg of harmine, and 892 mg of harmaline (THH not reported). Very high concentrations of harmaline and high harmaline/harmine ratios in Brazilian ayahuasca were reported by Pires *et al.* (Salum Pires et al. 2009) and these findings were noted as an exception by Souza *et al.* (Souza et al. 2019). In comparison with our results and results by Souza et al. (2019), it seems unlikely that a Brazilian religious group would add *P. harmala* to their sacrament or achieve such harmaline/harmine ratios in the brew using only *B. caapi* as a MAOI.

If the findings of very high concentrations of harmaline (exceeding concentrations of harmine in the same brew) in ayahuasca are not measurement or reporting errors, they may indicate use of *P. harmala* or harmaline-containing plant extracts as ayahuasca additives.

Concentrations of the analytes in different degrees of Daime

Measured concentrations of alkaloids in different grades of Daime were in good correspondence with users' empirical knowledge about the strengths of different grades of Daime. Increase of concentrations of the analytes and decline of THH/HME ratio with increasing grade of Daime from "*primeiro grau*" to "*mel*" were observed. Increase of concentrations of all the analytes corresponds to longer times of concentration of the brew by evaporation of water during boiling, and is related to overall strength of the brew and ceremonially used dosages. Decline of THH/HME ratio with the degree of Daime corresponds to longer boiling times and also to increasing number of repeated extractions of the same plant material during *feitio*, and may be related to different qualitative subjective effects of different degrees of Daime. This difference in subjective effects may be due to different degrees of MAO inhibition, or due to other biochemical differences between these compounds. THH is not a strong MAO inhibitor but it is a (weak) serotonin presynaptic uptake inhibitor (Callaway et al. 1999). Despite their structural similarity, the biochemical properties of THH and harmine are different. Callaway (1999, 267) noted about another ayahuasca-using church (*União do Vegetal*) that "*experienced drinkers seem to prefer those teas where THH concentrations were high, relative to harmine and harmaline.*" Our findings in Santo Daime confirm this observation. Callaway connected the variation of the relative concentration of THH in ayahuasca brews to its variability in *B. caapi*, our work shows that it may also depend on the preparation of the brew.

Differences between traditional and neoshamanic brews

Higher (in average by 48%, or even 55% if samples 15 and 25 are taken into account) and more variable concentrations of DMT in "neoshamanic" samples (compared to indigenous "shamanic" samples) may reflect use of higher and more variable proportions of DMT-containing admixture plants by neoshamanic facilitators. Significant correlations between concentrations of DMT and THH, also between their ratios to the concentration of harmine among shamanic and Daime samples may reflect following of traditional recipes with fixed proportions of constituent plants, and/or lesser variation of the chemical composition of their plant material compared to the diverse "neoshamanic" category. Use of admixtures and/or analog plants in various proportions and absence of traditional recipes may contribute to absence of such correlations among "neoshamanic" samples.

Ayahuasca cannot be reduced to the four analytes studied in this work. Several other bioactive compounds have been found in ayahuasca (Wang et al. 2010). These compounds may contribute to its effects.

Pharmahuasca with moclobemide, Mimosa and psilocin

From "ayahuasca ceremonies" held in Europe we got two samples containing moclobemide (a pharmaceutical MAOI antidepressant), psilocin, high concentrations of DMT from *Mimosa* (confirmed by the presence of yuremamine) and very low concentrations of *Banisteriopsis caapi* alkaloids. These brews were psychoactive due to the interaction of DMT with moclobemide that had been added as a MAOI to replace *B. caapi*, and an admixture containing psilocin. The brew presented stronger gastrointestinal side effects than ayahuasca

usually does. Participants were not informed about addition of moclobemide and psilocin to the brew.

Non-traditional additives in brews used in Europe

Summarizing, substitutions found in analyzed preparations from Europe included:

(1) ayahuasca analog ("anahuasca") containing *jurema* (*Mimosa tenuiflora*) as a source of DMT instead of (or in addition to) its traditional plant sources;
(2) ayahuasca analog containing Syrian rue (*Peganum harmala*) as a MAOI in addition or instead of *B. caapi*; and
(3) ayahuasca analogue with a pharmaceutical agent ("pharmahuasca"), in which *B. caapi* (or most of it) was replaced by moclobemide (a pharmaceutical MAOI), and other psychedelics (e.g. psilocin) were added to mimic the psychedelic effect of ayahuasca.

Peganum harmala (Syrian rue) and *Mimosa tenuiflora* (*jurema*) were used in neoshamanic ceremonies held in Europe. *P. harmala* was used as a substitute for *B. caapi* or a potentiating pre-treatment in ayahuasca ceremonies due to its content of harmaline as an MAOI. *Mimosa tenuiflora* was used as an alternative source of DMT in ayahuasca. Those plants are not used for Amazonian traditional ayahuasca, but they are used in Europe because they produce psychoactive effects similar to ayahuasca and are cheaper and easier to access in Europe than the traditional Amazonian plants.

Substitutions were made with partial informed consent of the participants: some participants were sometimes informed about them on their request either before or after the ceremony. However, the use of analog plants and substances was not communicated to participants proactively. Use of unknown substances in unknown quantities and non-traditional combinations at "ayahuasca ceremonies" is a considerable health risk and an ethical problem.

Effects of regulation and self-regulation

Legal uncertainties discourage communication about the composition of psychoactive remedies between facilitators and participants. Also, the fact that ayahuasca is illegal or has uncertain legal status in most European countries may encourage the substitution of the brew by a concoction made by other – legal or illegal – components.

No analogs were found among ayahuasca samples from Brazil or samples from Santo Daime ceremonies in Europe. Self-regulation and established ritual procedures of preparation that are open for participation of the members of the community seem to serve as a safeguard against adulteration and falsification.

Advice on user caution and user education by science-based and educational organizations like ICEERS and Chacruna.net, also evidence-based regulation and development of ethical standards (e.g. (Plantaforma 2009), "Code of Ethics for Spiritual Guides." n.d.) and (Ayahuasca Defense Fund n.d.)) could reduce risks caused by adulterated ayahuasca or ayahuasca analogs.

We recommend for ayahuasca users open inquiry and awareness about the constituents of the used brew, especially concerning ceremonies held outside of South America and its traditions. We recommend to avoid facilitators who do not inform participants clearly and pro-actively about the composition of the brew. People have the right and responsibility to know what they take, so that they can learn from their individual response to the substance, and the medical staff can be properly informed in case of an adverse reaction.

We see a need for the further development of evidence-based regulations and ethical self-regulations about the composition of the brew in collaboration between researchers and practitioners of ayahuasca rituals. As a minimum, we suggest that the organizer of the ceremony should pro-actively inform potential participants about the composition and origin of the brew, its expected effects and risks, also about use of non-traditional plants and substances in the brew (if these are used) before decisions to participate are made.

In ceremonies ayahuasca is often called "the medicine". As a powerful natural preparation revered by many of its users, ayahuasca certainly deserves clarity about its composition – at least at the same level as it is commonly expected of any medicinal product intended for human use.

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No potential conflict of interest was reported by the authors.

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