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Clay Villanueva

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

ARIZONA YAGÉ ASSEMBLY, NORTH AMERICAN ASSOCIATION OF VISIONARY CHURCHES, and CLAY VILLANUEVA, Plaintiffs, vs. WILLIAM BARR, Attorney General of the United States; UTTAM DHILLON, Acting Administrator of the U.S. Drug Enforcement Administration; CHAD F. WOLF, Acting Secretary of the Dept. of Homeland Security; MARK A. MORGAN, Acting Commissioner of U.S. Customs and Border Protection; THOMAS PREVOZNIK, Deputy Assistant Administrator of the DEA Dept. of Diversion Control, in his personal capacity; the UNITED STATES OF AMERICA; the STATE OF ARIZONA; MARK BRNOVICH, Arizona Attorney General; MARICOPA COUNTY, a political subdivision of the State of Arizona; and, MATTHEW SHAY, Defendants.	Case No.: 3:20-CV-03098-WHO DECLARATION OF PAULO CESAR RIBEIRO BARBOSA Date: September 9, 2020 Time: 2:00 P.M. Courtroom: 2 (17th floor)

Paulo Cesar Rebeiro Barbosa declares and affirms:

1. I am an Adjunct Professor in the Department of Philosophy and Human Sciences working in the field of Scientific Methodology at the State University of Santa Cruz in Ilheus, Brazil.

2. The CV attached as Appendix II is a true and correct statement of my qualifications to provide the opinions expressed in the Opinion Letter attached hereto as Exhibit 1.

3. During early 2018, I was retained by the Arizona Yagé Assembly ("AYA") to provide the summary of scientific evidence and expert opinions presented in the attached Opinion Letter. These opinions and the scientific evidence supporting those opinions are current as of this date, thanks in substantial part to the assistance of my co-professor Eduardo Ary Villela Marinho, who provided vital updates regarding research completed since April 2018. Because of the strength of his contributions, that brought my prior research and analysis up to date with the most recent research in this field, I have attached a copy of Prof. Marinho's CV as Appendix III. The additional research, easily identifiable in the Opinion Letter as citations to studies completed in 2018 – 2020, to which we of course had no access prior to publication. The additional research adds weight to the conclusions expressed in the Opinion Letter, particularly in the section analyzing whether Ayahuasca serves as, or stimulates consumption of, drugs of abuse.

4. The Opinion Letter addresses the questions that were presented to me for analysis and response, based on the scientific evidence summarized in the Opinion Letter remains as accurate today as it was when I signed it, and I currently hold all of the same opinions on the topics addressed in the Opinion Letter. During the two years that have passed since I signed the Opinion Letter, some additional information has come to my attention that warrants providing a brief update, however.

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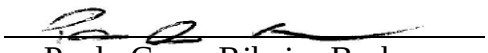
5. I may be contacted through AYA's attorney, and upon reasonable advance notice, will be available to answer questions via teleconference from here in Brazil.

I declare and affirm, pursuant to 28 U.S.C. § 1746(2), that the foregoing is true and correct, and that this declaration was signed on August 5, 2020, at Ilheus, Bahia, Brazil.



Paulo Cesar Ribeiro Barbosa

August 4, 2020

Dr. Paulo Cesar Ribeiro Barbosa
Prof. Adjunto do Departamento de Filosofia e Ciencias Humanas
Departamento de Filosofia e Ciências Humanas
Area de Metodologia Cientifica
Universidade Estadual de Santa Cruz - Ilhéus – BA
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To: United States District Court for the Northern District of California

Re: Application for Religious Freedom Exemption of Arizona Yagé Assembly

I have been retained by the Arizona Yagé Assembly ("AYA") to answer a series of questions regarding the traditional Amazonian brew known variously as ayahuasca, yage, and hoasca[1] to aid the United States Drug Enforcement Administration (the "Agency") in deciding whether to grant an exemption to AYA to practice religious ceremonies in which AYA members drink ayahuasca.
I have provided answers to these questions in the form of concise professional opinions in italics followed by an explanation of my opinion, supported by a summary of relevant studies. Appendix I summarizes some of the results of the studies discussed below in chart format.

My opinions are based on my professional education, my study of the available scientific research in the field, knowledge acquired through collaboration with other experts in the field, and my own research. Appendix II hereto is my curriculum vitae, stating my qualifications to render the opinions expressed herein.

I also adopt the conclusions of my co-researcher, Eduardo Ary Villela Marinho, who provided vital updates to a prior analysis I prepared approximately two years ago, that strengthens the conclusions expressed in this Opinion Letter, particularly in the section analyzing the evidence about whether Ayahuasca serves as, or stimulates abuse of, drugs of abuse. Because of the strength of his contributions, that brought my prior research and analysis up to date with the most recent research in this field, I have attached a copy of Prof. Marinho's CV as Appendix III.

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[1] Recipes for the brew can encompass a wide range of herbs, however, the most commonly used formulation for religious use is extracted from a combination of *Banisteriopsis Caapi* (harmaline, harmine, tetrahydroharmine, and other beta-carbolines) and a second herb containing Dimethyltryptamine, generally *Psychotria Viridis* or *Diplopterys Cabrerana*. Opinions expressed in this letter are expressed regarding this traditional "two-ingredient" brew, which is used by the UDV, the Santo Daime, and AYA.

Do ayahuasca and dimethyltryptamine have substantially different effects?

Yes. DMT is a psychedelic and, in humans, is usually administered intravenously, felt nearly instantaneously, and exhausts its powerful effects within under a half hour. Regarding intensity of effect, the effects of DMT are estimated to be twice as intense compared to equivalent dosages of ayahuasca. By comparison, ayahuasca is consumed orally, and its effects are slow and progressive, leading to a 4 - 6 hour experience that is more controllable than DMT.

DMT and ayahuasca are very different in their effects, with DMT being more intense and less subject to control than ayahuasca. Grob's seminal paper evaluated the "maximum intensity of the effects of DMT" as approximately twice that of ayahuasca at "equivalent doses." (Grob et al., 1996). The acute effects of DMT are very intense, appear nearly instantaneously after intravenous administration, and are over in under an hour (Strassman & Qualls, 1994; Strassman et al., 1994.) During the last few decades, clinical trials have been carried out on humans where both DMT (in purified form, administered intravenously) and ayahuasca (administered orally) have been administered in a laboratory context, and their acute effects have been characterized both at the psychological and somatic levels. Ayahuasca affects users slowly and progressively. Effects are felt 45 to 60 minutes after administration, reach their maximum effects 2 hours later, decline thereafter, and cease after 4 to 6 hours (Riba, 2003; dos Santos, 2011). Thus, the effects of ayahuasca are much more controllable than those of pure DMT.

Does ayahuasca adversely affect the physical health of religious ayahuasca users?

No. Ayahuasca is a non-toxic psychedelic tea whose main adverse physical effects are nausea and vomiting. It causes slight impact on the cardiovascular system. Religious ayahuasca use does not have adverse effects on physical health, and is associated with reduced physical pain and decreased impairment of life activities due to physical infirmities. Studies relevant to this topic are summarized in Chart A, Appendix I.

Toxicity is considered the capacity of a substance to cause harm to an organism by means of its chemical properties (Baños & Farré, 2002). From a toxicological viewpoint, the minimum psychoactive dose of a substance being administered to induce a psychoactive effect should be less than the toxic dose. This is certainly the case with ayahuasca, that has no toxic effects at all at dosage levels sufficient to induce a powerful psychoactive effect. It is thus a physically non-toxic psychedelic. This statement is subject to the caveat that persons taking MAO inhibitors should not take ayahuasca, and that pre-ceremonial dietary restrictions to avoid tyramine-containing substances should be observed.

The main adverse effects produced by ayahuasca are nausea and vomiting (Callaway, et al., 1999; Riba et al., 2001; Riba, 2003; Riba & Barbanoj, 2005; dos Santos, 2011; dos Santos et al., 2012). The emetic action of ayahuasca is

related first to the organoleptic properties of the decoction, and second to its serotonergic action (Callaway et al., 1999). The impact of ayahuasca on the cardiovascular system is minimal, producing only slight increases in blood pressure and heart rate that have no clinical implications (Riba et al., 2001, 2003; dos Santos et al., 2012). Studies to determine the acute effects of ayahuasca in the laboratory (Riba, 2003; dos Santos, 2011) and in natural contexts (McKenna, 2004), show that ayahuasca is physiologically safe.

Long-term Santo Daime users of religious ayahuasca showed significantly better scores than the control group on ASI-assessed Medical Status (Fabregas et al. 2010). Additionally, the UDV subjects showed improvement in the Bodily Pain subscale of SF-36 at six-month follow-up (Barbosa et al. 2009). Finally, UDV subjects scored better than the control group on a scale used to measure how much quality of life suffered from physical health restrictions -- the Medical Outcomes Study Short Form-36 (SF-36) Barbosa et al. (2016).

Does ayahuasca in the religious context serve as a drug of abuse or stimulate abuse of other drugs?

No. In my professional opinion, the scientific evidence does not support any hypothesis that religious use of ayahuasca constitutes or leads to drug abuse. Indeed, the reverse appears to be the effect. For many users, religious ayahuasca use diminishes or eliminates abuse of alcohol and other substances. I cite and briefly discuss the relevant results from five studies in support of this opinion.

Pre-clinical studies have found that in different mouse models of addiction-related behaviors, ayahuasca administered in doses between 100 and 300 mg/kg promotes important anti-addictive effects against the use of ethanol (Cata-Preta et al., 2018; Oliveira -Lima et al., 2015) and psychostimulants (methylphenidate, Reis et al., 2020). In addition, Reis et al., 2020 also demonstrated that, when administered after treatment with ethanol, ayahuasca reversed the changes in neuronal activity induced by methylphenidate in brain regions related to addiction, an effect that was maintained even after re-exposure to methylphenidate, suggesting an important role for ayahuasca in preventing drug-induced relapse. Cata-Preta et al. 2018 further demonstrated that when administered separately, extracts of the two main plant constituents of ayahuasca, *Banisteriopsis caapi* (which contains MAO-inhibiting Beta carbolines) and *Psychotria viridis* (which contains DMT), also showed anti-relapse effects in a model of ethanol reward.

Among the earliest studies to provide evidence of a lack of association between religious use of ayahuasca and behavior associated with drugs of abuse was Grob's seminal human assessment of religious users of ayahuasca. Grob's study reported zero (0) UDV members with current drug/alcohol-related problems, compared to one person with alcohol use disorder (AUD) in the non-ayahuasca-using control group (Grob et al., 1996). Grob's study was conducted in Brazil. Researchers administered the Composite International Diagnostic Interview (CIDI) to 15 adult long-term UDV members and 15 non-ayahuasca-user controls. Five (5) UDV members who suffered from AUD before becoming UDV members no longer had active AUD diagnoses. By comparison, only one control subject showed past and no longer active AUD diagnosis.

A larger study was completed in Brazil in 2010, and compared 127 ayahuasca drinkers with 115 control subjects, assessing them using the biopsychosocial criteria of the Addiction Severity Index 5th Edition (ASI-5, the standard drug-dependence assessment). The positive results were twofold: (1) no evidence of drug dependence among the ayahuasca drinkers, and (2) no association between continuous ritual use of ayahuasca and harmful biopsychosocial consequences related to drugs of abuse. As in the studies cited above, the ayahuasca group consumed less alcohol and other drugs than the control group. These scores on the biopsychosocial criteria for drug dependence were replicated a year later (Fábregas et al., 2010).

A study conducted at the University of New Mexico compared the substance-abusing behavior of members of the UDV church with that of church-going Christians. The two groups were comprised of 30 UDV ayahuasca users and 27 non-ayahuasca-using devout Catholics and Protestants (Barbosa et al., 2016). The UDV members drank ayahuasca in their twice-monthly church meetings. The Catholic and Protestant subjects attended masses and services more frequently than the UDV subjects. Relative to the control group, the UDV group demonstrated greater past intoxication-driven alcohol use and past use of cannabis, but less recent use of alcohol. Put simply, the UDV group started out with more marijuana and alcohol users, and ended up with fewer alcohol users. The control group numbers did not diminish for either category.

Doering-Silveira et al. (2005) administered a questionnaire based on the World Health Organization criteria for substance use and found lower past month and past year alcohol use in 41 Brazilian adolescent UDV ayahuasca users, compared to 43 matched control adolescents with no previous ayahuasca exposure.

The tendency of ayahuasca users to abandon alcohol and other drugs of abuse was again observed in a 2008 study of 32 Oregon Santo Daime members who were examined using the Structured Clinical Interview for DSM-IV psychiatric disorders (SCID). This group of ayahuasca users showed marked reduction in addictive behavior: Twenty-two (22) participants with a previous history of drug/alcohol-related problems were in full remission, one marijuana-dependent person was in partial remission, and one continued to abuse marijuana. (Halpern et al. 2008).

A large-scale survey was conducted with 1,947 members of UDV from all geographic areas of Brazil (Barbosa et al. 2018). The Substance Abuse and Mental Health Services (SAMHSA) questionnaire was administered to compare the lifetime use and current prevalence of alcohol and tobacco use disorders between the UDV and a national normative sample (n=7,939). The authors found that lifetime use of alcohol and tobacco was higher in UDV sample compared to the Brazilian norms for age ranges of 25–34and over 34 years old, but not for the age range of 18–24 years old. However, current prevalence for alcohol and tobacco use disorders were lower in the UDV sample than the Brazilian norms for all age ranges. This study also found that the more the participants attended ayahuasca rituals during their lifetime and during the previous 12 months, the less they used alcohol and tobacco during the previous year and month, and the less they had current alcohol and tobacco use disorders. The salient results of the cited studies are summarized as Chart B in Appendix I.

Does ayahuasca adversely affect the mental health of ceremonial ayahuasca users?

No. In my professional opinion, the scientific evidence does not support the hypothesis that ritual use of ayahuasca adversely affects mental health.

Concern for the health of the ayahuasca-using community has fueled considerable research into this topic, and the weight of the scientific evidence today indicates that religious ayahuasca users demonstrate less psychiatric morbidity, *i.e.,* mental illness, than either non-ayahuasca using control groups, or the general population. Using the CIDI to assess the mental health of ayahuasca users and compare it with that of non-users, Grob's seminal study identified no one in the UDV group with a current psychiatric diagnosis; whereas the control group included one person with hypochondriasis (Grob *et al*. 1996). Subsequent studies suggested that the rate of psychotic episodes that occured in ayahuasca ceremonial settings did not differ from the rate of general population (Lima and Tofoli 2011; Gable 2007). Moreover, the causal relationship of these episodes with ayahuasca intake were difficult to ascertain, because other risk factors, such as concurrent use of other substances and past history of psychosis, were present in most of the cases (Dos Santos et al. 2017).

These evaluations of the mental health effects ayahuasca intake within religious contexts are reinforced by a recent double-blind randomized placebo-controlled study (Palhano-Fontes et al. 2019). The authors found out that ayahuasca administration elicited rapid antidepressant effects, as assessed by the Montgomery-Åsberg Depression Rating scale (MADRS) and the Hamilton Depression Rating scale (HAM-D), in treatment-resistant depression patients.

Further, several studies show improved measures of mental health contemporaneously with continued religious ayahuasca use. The salient results of the cited studies are summarized in Chart C in Appendix I.

The Fabregas Study

Fabregas *et al*. (2010) found better scores on the psychiatric status subscale of the ASI-V among the Santo Daime group relative to non ayahuasca-using control groups.

The Doering-Silveira Study

Doering-Silveira *et al*. (2005) reported less anxiety symptoms using the State-Trait Anxiety Inventory (STAI), less body dysmorphism symptoms as assessed by Body Shape Questionnaire (BSQ), and less Attention Deficit Disorder using Conner's Adolescent Self-Rating scale than the control group.

The Halpern Study

Halpern *et al*. (2008) found that the Santo Daime group had fewer, less intense complaints, and lower levels of overall severity of symptoms than the normative group for the Symptom Check List Revised 90 (SCLR90).[2]

[2] The SCLR90 assesses three categories of symptoms: Positive Symptom Total (overall complaints), Positive Symptom Distress Index (intensity of complaints), and Global Severity Index (overall severity of complaints).

Ayahuasca users were found to be free of clinically significant anxiety as measured by the Hamilton Anxiety Rating Scale (0/32 on the HAM-A)

Ayahuasca users demonstrated a low rate of depression as measured by Hamilton Depression Rating Scale (1/32 on the HAM-D). This was particularly significant, because five of the ayahuasca users had suffered at least one major depressive disorder before joining Santo Daime, as revealed by administration of the Structured Clinical Interview for DSM-IV Disorder (SCID).

The SCID also identified one individual with a current bipolar I disorder, one with a current panic disorder, six with recurrent major depressive disorders, with four in remission and two in partial remission, and two with simple phobia disorder in partial remission, four with simple phobia (two in remission and two in partial remission), three with bulimia nervosa in remission, six with posttraumatic stress disorder or panic disorder in remission. Eight subjects reported remission occurring after their involvement in ayahuasca religious use.

The Barbosa Study

Barbosa *et al*. (2009) prospectively assessed psychiatric morbidity in new ayahuasca users using the Clinical Interview Schedule – revised edition (CIS-R), which was administered to each subject three times: shortly before, a week after, and six months after the subjects' first religious ayahuasca experience. Nineteen (19) of the subjects were members of the Santo Daime, and nine (9) were from the UDV.

The Santo Daime group nearly met criteria for the CIS-R defined psychiatric disorder (scores of at least 12) before drinking ayahuasca. Their scores significantly improved at one week and six-month follow-up (11.6 before ayahuasca, 5.1 a week later and six-months later).

The UDV group scored below the cut off value for CIS-R defined psychiatric disorder before beginning participation and showed no significant changes at either one-week or six-month follow-up.

In Barbosa et al's 2016 study at the University of New Mexico, the UDV group scored lower than the active religious control group for depression and confusion as assessed by the Profile of Mood States (POMS).

Does religious use of Ayahuasca have adverse effects on cognitive function?

No. In my professional opinion, the scientific evidence discussed below and summarized in Chart D indicates that religious use of ayahuasca does not negatively affect human cognitive function.

Grob et al. (1996) used the WHO-UCLA Auditory Verbal Learning Test (WHO UCLA-AVLT) to compare the memory functions of long-term UDV members with those of a matched control group. The WHO UCLA-AVLT test assesses mild degrees of cognitive dysfunction and consists of several trials of recalling words read from lists of common items such as household objects. The authors detected better performance in ayahuasca users in the recall of words for the fifth learning trial.

Two more recent studies administered a comprehensive battery of neuropsychological tests to compare the attention, psychomotor speed, verbal

and visual abilities, memory, and mental flexibility of non-ayahuasca using control groups with those of UDV adolescents (Doering-Silveira et al. 2005), and UDV and Santo Daime adults (Bouso et al. 2012; Barbosa et al. 2016). Bouso et al. (2012) found better results on cognitive performance of Santo Daime group relative to the control group. No difference in cognitive functions were found in UDV adolescents and adults relative to their control group (Doering-Silveira et al. 2005; Barbosa et al. 2016).

Conclusion

Ayahuasca and dimethyltryptamine are two very different psychoactive substances, and of the two, ayahuasca is far more amenable to conscious control. Ayahuasca is essentially an herbal tea that often induces nausea and vomiting due to its organoleptic and serotonergic characteristics. Other physical effects include mild rises in blood pressure and heart rate. The psychoactive effects begin slowly after a 45-minute period of onset, and end within approximately six hours. Ayahuasca consumed in a religious context is not being used as a drug of abuse, nor does the religious use of ayahuasca lead to the abuse of other drugs; instead, religious ayahuasca users generally abandon abuse of alcohol after they become members of an ayahuasca church. These data are backed up by pre-clinical evidence indicating that ayahuasca blocks many abuse-related behavioral effects of drugs of abuse. Ayahuasca does not adversely affect mental health. Many religious ayahuasca users start out with greater psychological morbidity than the control groups, and show a marked improvement with years of ayahuasca use, reporting greater mental health after participating in religious ayahuasca use compared to control groups. Ayahuasca has not been observed to impair cognitive function, and on some testing scales, is associated with improved functioning.

Very truly yours,

Paulo Cesar Ribeiro Barbosa

APPENDIX I

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APPENDIX I

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Riba dos Santos	Physiological measures of acute effects	Minimal impact on the cardiovascular system Slight increases in blood pressure and heart rate that have no clinical implications
Fabregas	ASI-5 medical status	Santo Daime had better results than the control group
Barbosa	SF-36	Improved Bodily Pain six months after the first ayahuasca experience in UD
Barbosa	SF-36	UD had better score on domain role limitations due to physical health than the control group

d		
Grob	CIDI	UD have less current substance use disorder than control group Past diagnostic criteria for alcohol use disorders (AUD) for 5 UD members who no longer met the criteria after becoming UD members.
Fabregas	ASI-5	o evidence of drug dependence in Santo Daime group, nor evidence that the continuous ritual use of ayahuasca was associated with harmful biopsychosocial consequences related to drugs of abuse. Moreover, the Santo Daime ayahuasca group consumed less alcohol and other drugs compared to the control group
Doering-Silveira	World Health Org. criteria	UD adolescent members had less past year and month use of alcohol relative to the control group
Halpern	SCID - DSM-I	Participants of Santo Daime with a previous history of drug alcohol-related problems were in full remission
Barbosa	ASI-5	UD Had More Prior intoxication-driven alcohol use Use than control group UD Had Less Recent Use of alcohol than control group

d		
Grob	CIDI	UD have less current psychiatric diagnoses than controls
Fabregas	ASI-	Santo Daime had better scores on the psychiatric status than controls
Doering-Silveira	STAI	UD adolescent group had less anxiety symptoms than the control group
Doering-Silveira	BS	UD adolescent group had less body dysmorphism symptoms than the control group

APPENDIX I

Doering-Silveira	Conner's Adolescent Self-Rating	UD adolescent group had less attention deficit disorder than the control group
Halpern	SCLR-90	Santo Daime group had better scores than the normative group for Positive Symptom Total, Positive Symptom Distress Index and Global Severity Index
Halpern	HAM-A	Santo Daime group was free of clinically significant anxiety (0 32)
Halpern	HAM-D	Santo Daime group demonstrated a low rate of depression (1 32)
Halpern	SCID	Eight Santo Daime subjects reported remission of psychiatric disorder occurring after their involvement in ayahuasca religious use.
Barbosa	CIS-R	ew Santo Daime parcicipants reported improved scores on minor psychiatric symptoms six months after drinking ayahuasca o difference in the scores of minor psychiatric symptoms in new ayahuasca users within UD
Barbosa	POMS	UD had less depression than the active religious control group UD had less confusion than the active religious control group

d		
Grob	WHO-UCLA A LT	UD had better performance the recall of words for the fifth learning trial
Doering-Silveira	Comprehensive battery of neuropsychological function	o difference between UD adolescents and control group
Barbosa	Comprehensive battery of neuropsychological function	o difference between UD adults and control group
Bouso	Comprehensive battery of neuropsychological function	Santo Daime had better results on cognitive function than the control group

APPENDIX II

Biography

Dr. Paulo Cesar Ribeiro Barbosa obtained his Ph.D. in Medical Sciences at Universidade Estadual de Campinas (UNICAMP) in 2008 working on a follow-up evaluation of religious ayahuasca users. He obtained his degree in Social Sciences at Universidade de São Paulo (USP) in 1992 and a degree in Psychology at Faculdade de Ilhéus (CESUPI) IN 2019. Since 2001 he has worked on a variety of projects involving psychiatric, psychological, neurocognitive, social and cultural assessments of ayahuasca users within Brazilian and North-American urban contexts. Dr Barbosa was appointed Professor of Scientific Methods in 2002 in the Departamento de Filosofia e Ciências Humanas at Universidade Estadual de Santa Cruz (Brazil). He worked as Adjunct Assistant Professor at the Psychiatry Department of University of New Mexico. Dr. Barbosa's main research activities concern the relationships among psychiatric, psychological and anthropological methods of evaluating the effects of ayahuasca in Brazilian and North-American urban settings.

Research Strategy and Context

Ayahuasca is a hallucinogenic beverage produced from Amazonian plant components that contain harmine, harmaline, tetrahydroharmine and N,N-dimethyltryptamine (DMT). The ritually sanctioned use of the brew is widespread among Amerindian and Mestizo groups of the western Amazonian basin. Ethnological data suggest that the ritual and ideological framework accompanying the use of ayahuasca in these societies can minimize social and psychological problems associated with the use of psychoactive substances in western societies.

During the last three decades modern urban Brazilian ayahuasca religions, such as *União do Vegetal* and *Santo Daime* who use ayahuasca as a key element in their doctrines and ceremonial meetings have spread from the Amazon to major cities in Brazil, as well as to Europe and North America. Hallucinogens are often associated by mainstream psychiatry with psychopathology and abuse potential and the fact that their use is restricted legally the expanded use of the beverage has brought these religious groups under scrutiny by law enforcement officials. On the other hand, ayahuasca religions claim that the brew can show therapeutic properties for the treatment of several psychological, psychiatric and general health problems.

Many ethnographic studies have been conducted in the attempt to describe the social and ideological structures involved in these religious groups concerning the purported therapeutic use of ayahuasca. However, rigorous scientific evaluations about its actual effects on health are still lacking.

This research programme addresses the need for rigorous scientific investigations when evaluating the effects of ayahuasca on mental health and the inter-relationships between ritual and social network involved in religious ayahuasca groups in determining the health status of urban ayahuasca users. The aims of the research strategy are:

- To evaluate the socioeconomic profile of people who seek ayahuasca experiences and to elicit their therapeutic and religious itineraries;
- To elicit how people evaluate and interpret their ayahuasca experience;
- To evaluate the effects of ayahuasca use on psychiatric symptoms;

- To evaluate the effects of ayahuasca use on personality traits;
- To evaluate the effects of ayahuasca use on neurocognitive functions;
- To evaluate the effects of ayahuasca use on health-related quality of life;
- To evaluate the effects of ayahuasca use on licit and illicit drug use and abuse;
- To evaluate the interaction of ayahuasca use with selective serotonin reuptake inhibitors.

Ongoing research protocols

1) Quality of life and drug use in UDV adepts

This project proposes to evaluate the quality of life and use and abuse of licit (such as alcohol and tobacco) and illicit (e.g., cocaine, marihuana) drugs in adepts of the União do Vegetal. It will also evaluate the potential adverse interaction between ayahuasca and serotonergic antidepressant drugs. In order to achieve these goals, we will conduct a national survey using a standardized instrument of WHO on the quality of life (WHOQOLBref), and two standardized instruments based on the WHO and the Substance Abuse and Mental Health Services (SAMHSA), to assess drug use and addiction. The independent variables will be the frequency pattern of ayahuasca use and the years and months of joining the religion. We investigate whether subjects who attend ayahuasca rituals regularly show improved quality of life and drug use in comparison with those who attend these rituals intermittently. Length of time of regular attendance to these rituals will also be correlated with the corresponding measures. It is also aimed to investigate whether the use of medications and the frequency pattern of ritual attendance is associated with adverse reactions during the acute effects of ayahuasca. Additionally, there will be a qualitative research on health and welfare of members of the UDV, in which respondents of the questionnaires will also be invited to take part in a qualitative follow-up study in order to assess the impact of religion on health.

Funded by National Counsel for Scientific Development (Federal Administration – Brazil)
Started: April 2009
Scheduled conclusion: March 2011
Coordinator: Paulo Cesar Ribeiro Barbosa
Researchers: Michael Winkelman, Alberto Groisman, Luis Fernando Tofoli

2) Personality traits, cognitive functions and drug abuse-related problems associated with regular ayahuasca use

It was aimed to evaluate potential drug abuse-related problems, personality traits and cognitive functions associated with regular ayahuasca use. Standardized instruments were used in order to assess a number of personality traits, cognitive functions and medical and psychosocial consequences of drug misuse in the following groups: a) a group of jungle-based ayahuasca users (n = 56) vs. non-ayahuasca-using rural group (n

= 56); and b) a group of urban-based ayahuasca users (n = 71) vs. a group of urban non-users (n = 59).

Funded by: Instituto de Etnopsicología Amazónica Aplicada (IDEAA).
Coordinator: Jose Carlos Bouso
Researchers: Josep Maria Fábregas, Débora González, Sabela Fondevila, Marta Cutxet, Xavier Fernández, Paulo César Ribeiro Barbosa, Miguel Ángel Alcázar-Córcoles, Jordi Riba

3) A psychological and neuropsychological evaluation of Hoasca users within Uniao do Vegetal in the USA

Hoasca is a hallucinogenic brew originally used for magico-religious purposes by Amerindian populations of the western Amazon Basin. Throughout the last four decades, Brazilian syncretic churches, such as Santo Daime and Uniao do Vegetal (UDV) have helped spread the ritual use of hoasca abroad. This trend has raised concerns that regular use of this N,N-dimethyltryptamine-containing tea may lead to the mental and physical health problems associated with drug abuse. Lawsuits involving tensions between drug control laws and principles of religious freedom had occurred in Europe and in the USA. In 2006 the U.S. Supreme Court ruled for the UDV, allowing its local branch in the state of New Mexico to import, store and use hoasca. In 2009 the District Court of the State of Oregon ruled a similar decision in favor of a local branch of the Santo Daime Church. These decisions point to a significant increase in the use of hoasca in the U.S. and to the definitive establishment of this practice in American religious diversity. The few rigorous studies that have been completed on the psychological and medical effects of hoasca suggest mostly positive effects of religious hoasca use, but concerns about the potential for harmful effects remain. To further elucidate the effects of religious use of hoasca we propose a case-control study in which 35 North American users of hoasca within UDV will be compared to 35 matched control subjects with no history of hoasca use. The assessment will include instruments on quality of life, personality, spirituality and religiosity, mood, neuropsychological function and altered states of consciousness.

List of Publications

Full Articles

REIS, H. S.; RODRIGUES, I. R. S.; ANJOS-SANTOS, A.; LIBARINO-SANTOS, M.; SERRA, Y. A.; CATA-PRETA, E. G.; OLIVEIRA-CAMPOS, D.; KISAKI, N. D.; BARROS-SANTOS, T.; YOKOYAMA, T. S.; CRUZ, F. C.; OLIVEIRA-LIMA, A. J.; **BARBOSA, P. C. R.**; BERRO, L. F.; MARINHO, E. A. V. **Ayahuasca blocks the reinstatement of methylphenidate-induced conditioned place preference in mice: behavioral and brain Fos expression evaluations.** Psychopharmacology (Berl). 2020 Jul 16. DOI: 10.1007/s00213-020-05609-6. (Online ahead of print.)

BARBOSA, P. C. R.; TOFOLI, L. F.; BOGENSCHUTZ, M. P.; HOY, R.; BERRO, L. E. M.; ARECO, K.; WINKELMAN, M. **Assessment of alcohol and tobacco use disorders among religious users of ayahuasca.** Frontiers in Psychiatry, v. 9, p. 136, 2018.

CATA-PRETA, E. G.; SERRA, Y. A.; MOREIRA-JUNIOR, E. D. C.; REIS, H. S.; KISAKI, N. D.; LIBARINO-SANTOS, M.; SILVA, R. R. R.; BARROS-SANTOS, T.; SANTOS, L. C.; **BARBOSA, P. C. R.**; COSTA, J. L.; OLIVEIRA-LIMA, A. J.; BERRO, L. F.; MARINHO, E. A. V. **Ayahuasca and Its DMT- and β-carbolines - Containing Ingredients Block the Expression of Ethanol-Induced Conditioned Place Preference in Mice: Role of the Treatment Environment.** Frontiers in Pharmacology, v. 9, p. 561, 2018.

BARBOSA, P. C. R.; STRASSMAN, R.; SILVEIRA, D. X.; ARECO, K.; HOY, R.; POMMY, J.; THOMA, R.; BOGENSCHUTZ, M. P. **Psychological and neuropsychological assessment of regular hoasca users.** Comprehensive Psychiatry (Print), v. 71, p. 95-105, 2016.

BOGENSCHUTZ, M. P.; FORCEHIMES, A.; POMMY, J.; WILCOX, C.; **BARBOSA, P. C. R.**; STRASSMAN, R. **Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study.** Journal of Psychopharmacology (Oxford), v. 29, p. 1-11, 2015.

OLIVEIRA-LIMA, A.; SANTOS, R.; HOLLAIS, A.; GERARDI-JUNIOR, C.; BALDAIA, M.; WUO-SILVA, R.; YOKOYAMA, T. S.; COSTA, J.; MALPEZZI-MARINHO, E.; **BARBOSA, P. C. R.**; BERRO, L.; FRUSSA-FILHO, R. **Effects of ayahuasca on the development of ethanol-induced behavioral sensitization and on a post-sensitization treatment in mice.** Physiology & Behavior, p. 28, 2015.

BARBOSA, P. C. R.; MIZUMOTO, S.; BOGENSCHUTZ, M. P.; STRASSMAN, R. **Health status of ayahuasca users.** Drug Testing and Analysis, v. 4, p. 1, 2012.
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BOUSO, J. C.; GONZALEZ, D.; FONDEVILA, S.; CUTCHET M.; FERNÁNDEZ, X.; **BARBOSA, P. C. R.**; ALCÁZAR-CÓRCOLES, M. Á.; ARAUJO, W. S.; BARBANOJ, M. J.; FÁBREGAS J. M.; RIBA, J. **Personality, psychopathology, life attitudes and neuropsychological performance among ritual users of ayahuasca.**

Plos One, v. 7, p. 1-13, 2012.

ANDERSON, B.; LABATE, B. C.; MEYER, M.; TUPPER, K.; **BARBOSA, P. C. R.**; GROB, C.; DAWSON, A.; MCKENNA, D. **Statment on ayahuasca.** International Journal on Drug Policy, v. 23, p. 173-175, 2012.

MIZUMOTO, S.; SILVEIRA, D. X.; **BARBOSA, P. C. R.**; STRASSMAN, R. **HRS - Hallucinogen Rating Scale - Versão Brasileira: Tradução e adaptação transcultural.** Revista de Psiquiatria Clínica (USP. Impresso), v. 38, p. 231-237, 2011.

FÁBREGAS J. M.; GONZALEZ, D.; FONDEVILA, S.; CUTCHET M.; FERNÁNDEZ, X.; **BARBOSA, P. C. R.**; ALCÁZAR-CÓRCOLES, M. Á.; BARBANOJ, M. J.; RIBA, J.; BOUSO, J. C. **Assessment of addiction severity among ritual users of ayahuasca.** Drug and Alcohol Dependence, v. 1, p. 257-261, 2010.

BARBOSA, P. C. R.; CAZORLA, I. M.; GIGLIO, J. S.; STRASSMAN, R. **A six-month prospective evaluation of personality traits, psychiatric symptoms and quality of life in ayahuasca-naïve subjects.** Journal of Psychoactive Drugs 41 (3): 205-212, 2009.

BARBOSA, P. C. R.; DALGALARRONDO, P.; GIGLIO, J. S. **Altered States of Consciousness and Short-term Psychological After-effects Induced by the First Time Ritual Use of Ayahuasca in Urban Context in Brazil.** Journal of Psychoactive Drugs 37 (2): 193-201, 2005.

BARBOSA, P. C. R. O uso ritual de um alucinógeno no contexto urbano: estados alterados de consciência e efeitos em curto prazo induzidos pela primeira experiência com a ayahuasca. Jornal Brasileiro de Psiquiatria 52 (3): 181-190, 2003.

Book Chapter

LABATE, B. C.; SANTOS, R. G.; ANDERSON, B.; MERCANTE, M.; **BARBOSA, P. C. R.** The Treatment and Handling of Substance Dependence with Ayahuasca: Reflections on Current and Future Research. In: LABATE, B. C.; MACRAE, E. (org.). **Ayahuasca, Ritual and Religion in Brazil. Ayahuasca, Ritual and Religion in Brazil.** Londres: Equinox, 2010, v. , p. 205-227.

BARBOSA, P. C. R.; DA SILVA DOS SANTOS, S. F. Aspectos culturais e sociais da saúde mental. In: SILVA, C. P. B. V.; SOARES, E. F. S.; DOS SANTOS, J. E. (org.). **I Encontro de Saúde Mental: rede de experiências.** 1ª ed. Salvador: EDUNEB v. I, p. 51-59, 2007.

APPENDIX III

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Professional Biography of Dr. Eduardo Ary Villela Marinho

Dr. Eduardo Ary Villela Marinho obtained his bachelor's degree in Biological Sciences in the Pontifícia Universidade Católica de Campinas (1992) and his master's degree in Biological Sciences (Physiology) at at Universidade Estadual de Campinas (1997). He also holds PhD in Pharmacology at Universidade Federal de São Paulo (2011). Dr. Marinho was appointed Professor of Pharmacology at Universidade Estadual de Santa Cruz (Brazil). Dr. Marinho's main research activities concern Pharmacology and Physiology, Behavioral Pharmacology, Preference Conditioned by Place, Substance Abuse, Ayahuasca and other native medicinal plants.

Research Strategy and Context

1- Experimental therapeutic evaluation with Ibogaine in drug-induced chemical dependence in mice.
2- The role of 5HT2A receptors in the anti-addictive effect of Ayahusca in animal models of ethanol dependence.

List of Publications

1. REIS, HENRIQUE S.; RODRIGUES, ISA R. S.; ANJOS-SANTOS, ALEXIA; LIBARINO-SANTOS, MATHEUS; SERRA, YASMIM A.; CATA-PRETA, ELISÂNGELA G.; OLIVEIRA-CAMPOS, DANIELLA; KISAKI, NATALI D.; BARROS-SANTOS, THAÍSA; YOKOYAMA, THAIS S.; CRUZ, FABIO C.; OLIVEIRA-LIMA, ALEXANDRE J.; BARBOSA, PAULO C. R.; BERRO, LAIS F.; MARINHO, EDUARDO A. V.

Ayahuasca blocks the reinstatement of methylphenidate-induced conditioned place preference in mice: behavioral and brain Fos expression evaluations. PSYCHOPHARMACOLOGY. Fator de Impacto(2018 JCR): 3,4240, v.1, p.1 - , 2020.

2. BARROS-SANTOS, THAÍSA; SILVA, KALLYANE SANTOS OLIVEIRA; LIBARINO-SANTOS, MATHEUS; REIS, HENRIQUE SOUSA; Tamura, Eduardo Koji; DE OLIVEIRA-LIMA, ALEXANDRE JUSTO; BERRO, LAÍS FERNANDA; UETANABARO, ANA PAULA TROVATTI; MARINHO, EDUARDO ARY VILLELA

Effects of chronic treatment with new strains of Lactobacillus plantarum on cognitive, anxiety- and depressive-like behaviors in male mice. PLoS One. Fator de Impacto (2018 JCR): 2,7760, v.15, p.e0234037 - , 2020.

3. LIBARINO-SANTOS, MATHEUS; DE SANTANA SANTOS, ANA CATHERINE GOMES; CATA-PRETA, ELISANGELA G.; BARROS-SANTOS,

THAÍSA; NUNES BRANDÃO, NINA ROSA; BORGES, AUREA LORENA NUNES; SANTOS-BALDAIA, RENAN; HOLLAIS, ANDRÉ W.; BALDAIA, MARILIA A.; BERRO, LAÍS F.; Marinho, Eduardo A.V.; Frussa-Filho, Roberto; OLIVEIRA-LIMA, ALEXANDRE J.

Role of the treatment environment in the effects of aripiprazole on ethanol-induced behavioral sensitization and conditioned place preference in female mice. DRUG AND ALCOHOL DEPENDENCE. Fator de Impacto(2018 JCR): 3,4660, v.208, p.107856 - , 2020.

4. BRANDÃO, N.R.N.; LIBARINO-SANTOS, M.; MARINHO, E.A.V.; OLIVEIRA, T.S.; BORGES, A.L.N.; OLIVEIRA, A.P.; OLIVEIRA-CAMPOS, D.; AZEVEDO-SOUZA, N.; SANTOS, V.F.L.; BERRO, L.F.; OLIVEIRA-LIMA, A.J.

Treatment with zolpidem after ethanol administration potentiates the expression of ethanol-induced behavioral sensitization in mice. Brazilian Journal of Medical and Biological Research (on line). Fator de Impacto(2018 JCR): 1,8500, v.53, p.1 - 6, 2020.

5. MALPEZZI-MARINHO, ELENA L. A.; MOLSKA, GRAZIELA R.; FREIRE, LYVIA I. G. P.; SILVA, CRISTIANE I.; TAMURA, EDUARDO K.; BERRO, LAÍS F.; PARADA, CARLOS A.; MARINHO, EDUARDO ARY VILLELA

Effects of hydroalcoholic extract of Solidago chilensis Meyen on nociception and hypernociception in rodents. BMC Complementary and Alternative Medicine. Fator de Impacto(2018 JCR): 2,4790, v.19, p.72 - , 2019.

6. WUO-SILVA, RAPHAEL; FUKUSHIRO-LOPES, DANIELA F.; FIALHO, BRUNO P.; HOLLAIS, ANDRÉ W.; SANTOS-BALDAIA, RENAN; MARINHO, EDUARDO A. V.; MÁRI-KAWAMOTO, ELISA; YOKOYAMA, THAÍS S.; LOPES-SILVA, LEONARDO B.; BERRO, LAÍS F.; FRUSSA-FILHO, ROBERTO; LONGO, BEATRIZ M.

Participation of Dopamine D1 and D2 Receptors in the Rapid-Onset Behavioral Sensitization to Modafinil. Frontiers in Pharmacology. Fator de Impacto (2018 JCR): 3,8450, v.10, p.1 - 9, 2019.

7. BARBOSA, PAULO CESAR RIBEIRO; TÓFOLI, LUÍS F.; BOGENSCHUTZ, MICHAEL P.; HOY, ROBERT; BERRO, LAIS F.; MARINHO, EDUARDO A. V.; ARECO, KELSY N.; WINKELMAN, MICHAEL J.

Assessment of Alcohol and Tobacco Use Disorders Among Religious Users of Ayahuasca. Frontiers in Psychiatry. Fator de Impacto(2018 JCR): 3,1610, v.9, p.1 - 12, 2018.

8. CATA-PRETA, ELISANGELA G.; SERRA, YASMIM A.; MOREIRA-JUNIOR, ELISEU DA C.; REIS, HENRIQUE S.; KISAKI, NATALI D.; LIBARINO-

SANTOS, MATHEUS; SILVA, RAIANY R. R.; BARROS-SANTOS, THAÍSA; SANTOS, LUCAS C.; BARBOSA, PAULO C. R.; COSTA, JOSÉ L.; OLIVEIRA-LIMA, ALEXANDRE J.; BERRO, LAIS F.; MARINHO, EDUARDO A. V.

Ayahuasca and Its DMT- and β-carbolines - Containing Ingredients Block the Expression of Ethanol-Induced Conditioned Place Preference in Mice: Role of the Treatment Environment. Frontiers in Pharmacology. Fator de Impacto(2018 JCR): 3,8450, v.9, p.1 - 14, 2018.

9. SILVA, ALINE A.F.; SOUZA, EVELYN B.; CARVALHO, CASSIO C.; SILVA, RAIANY R.R.; BRITO, ANA CAROLINA L.; PRETA, ELISANGELA G.C.; OLIVEIRA, THAYNARA S.; BERRO, LAIS F.; OLIVEIRA-LIMA, ALEXANDRE J.; MARINHO, EDUARDO A.V.

Context-dependent effects of rimonabant on ethanol-induced conditioned place preference in female mice. DRUG AND ALCOHOL DEPENDENCE. Fator de Impacto(2018 JCR): 3,4660, v.179, p.317 - 324, 2017.

10. OLIVEIRA-LIMA, A.J.; MARINHO, E. A. V.; SANTOS-BALDAIA, R.; HOLLAIS, A. W.; BALDAIA, M. A.; TALHATI, F.; Ribeiro, Luciana T.C.; WUO-SILVA, R.; BERRO, L. F.; Frussa Filho, R.

Context-dependent efficacy of a counter-conditioning strategy with atypical neuroleptic drugs in mice previously sensitized to cocaine. PROGRESS IN NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY. Fator de Impacto(2018 JCR): 4,3150, v.73, p.49 - 55, 2017.

11. MARINHO, Eduardo A.V.; OLIVEIRA LIMA, ALEXANDRE J.; YOKOYAMA, THAIS S.; SANTOS-BALDAIA, RENAN; Ribeiro, Luciana T.C.; BALDAIA, MARILIA A.; DA SILVA, RAPHAEL WUO; HOLLAIS, ANDRE WILLIAN; TALHATI, FERNANDA; LONGO, BEATRIZ MONTEIRO; BERRO, LAIS FERNANDA; FRUSSA-FILHO, ROBERTO

Post-sensitization treatment with rimonabant blocks the expression of cocaine-induced behavioral sensitization and c-Fos protein in mice. PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR. Fator de Impacto(2018 JCR): 2,7730, v.156, p.16 - 23, 2017.

12. OLIVEIRA-LIMA, A.J.; SANTOS, R.; HOLLAIS, A. W.; GERARDI-JUNIOR, C. A.; BALDAIA, M. A.; WUO-SILVA, R.; YOKOYAMA, T.S.; COSTA, J. L.; MALPEZZI-MARINHO, E. L. A.; RIBEIRO-BARBOSA, P. C.; BERRO, L.F.; FRUSSA-FILHO, R.; MARINHO, E. A. V.

Effects of ayahuasca on the development of ethanol-induced behavioral sensitization and on a post-sensitization treatment in mice. PHYSIOLOGY & BEHAVIOR. Fator de Impacto(2018 JCR): 2,6350, v.142, p.28 - 36, 2015.

13. MARINHO, Eduardo A.V.; OLIVEIRA-LIMA, ALEXANDRE J.; SANTOS, RENAN; HOLLAIS, ANDRÉ W.; BALDAIA, MARILIA A.; Wuo-Silva, Raphael; YOKOYAMA, THAIS S.; TAKATSU-COLEMAN, ANDRÉ L.; PATTI, CAMILLA L.; LONGO, BEATRIZ M.; BERRO, LAÍS F.; Frussa-Filho, Roberto

Effects of rimonabant on the development of single dose-induced behavioral sensitization to ethanol, morphine and cocaine in mice. PROGRESS IN NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY. Fator de Impacto(2018 JCR): 4,3150, v.58, p.22 - 31, 2015.

14. PAULA FREIRE, L. I. G.; MALPEZZI-MARINHO, E. L. A.; MOLSKA, G. R.; Kohn, D.O.; CORREA, L.; MARINHO, E. A. V.

Evaluation of the Acute Toxicity of the Hydroalcoholic Extract of Solidago chilensis Meyen (Arnica Do Campo) in Mice. American Journal of Phytomedicine and Clinical Therapeutics. , v.2, p.217 - 228, 2014.

15. MARINHO, EDUARDO A. V.; OLIVEIRA-LIMA, ALEXANDRE J.; Wuo-Silva, Raphael; SANTOS, RENAN; BALDAIA, MARILIA A.; HOLLAIS, ANDRÉ W.; LONGO, BEATRIZ M.; BERRO, LAÍS F.; Frussa-Filho, Roberto

Selective action of an atypical neuroleptic on the mechanisms related to the development of cocaine addiction: a pre-clinical behavioural study. INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY. Fator de Impacto(2018 JCR): 4,2070, v.17, p.613 - 623, 2014.

16. PROCÓPIO-SOUZA, ROBERTA; FUKUSHIRO, DANIELA F.; TROMBIN, THAÍS F.; SILVA, R. W.; ZANLORENCI, LINEANE H.F.; LIMA, ALEXANDRE J.O.; RIBEIRO, LUCIANA T.C.; CORRÊA, JUSSARA M.R.M.; MARINHO, E. A. V.; KAMEDA, SONIA R.; ANDERSEN, MONICA L.; TUFIK, SERGIO; FRUSSA-FILHO, ROBERTO

Effects of group exposure on single injection-induced behavioral sensitization to drugs of abuse in mice. Drug and Alcohol Dependence. Fator de Impacto(2018 JCR): 3,4660, v.118, p.349 - 359, 2011.

17. TAMURA, EDUARDO KOJI; JIMENEZ, RENATA SPADA; WAISMAM, KALINE; GOBBO-NETO, LEONARDO; LOPES, NORBERTO PEPORINE; MALPEZZI-MARINHO, ELENA A.L.; MARINHO, EDUARDO A.V.; FARSKY, SANDRA H.P.

Inhibitory effects of Solidago chilensis Meyen hydroalcoholic extract on acute inflammation. JOURNAL OF ETHNOPHARMACOLOGY. Fator de Impacto(2018 JCR): 3,4140, v.122, p.478 - 485, 2009.