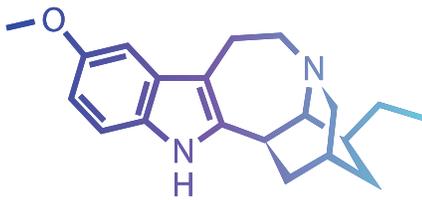




The Case of Brazil

After Ayahuasca, Ibogaine Opens Up Opportunity for First-Class Research in the Global South

Marcelo Leite, Ph.D.



Molecular compound of ibogaine

Ask researchers active in psychedelic science which three top countries publishing papers with the greatest annual citation rates in the biomedical field, and chances are, they will give you at least two right answers: the United States and the United Kingdom (UK), of course. Some would possibly rank Switzerland or Netherlands third, and they would be in the wrong; Brazil comes before them.

To be precise, both Brazil and Switzerland scored five articles each in the list, totaling 50 items compiled by David Wyndham Lawrence, Bhanu Sharma, Roland R. Griffiths, and Robin Carhart-Harris (Lawrence et al, 2021). However, a study carried out in Natal, in the state of Rio Grande do Norte (Northeastern Brazil), amassed 76 citations in just two years after its publication in 2019 (Palhano-Fontes et al., 2019), an average of 38 per year that put it in sixth place (the first Swiss paper appears in the twentieth position).

It might come as unexpected that an investigation originating in one of the poorest regions of the big South American nation would rank that high. Those in the know are not surprised, though, because we are talking of the first randomized placebo-controlled trial of a psychedelic substance (ayahuasca, in this case) to confirm a rapid antidepressant effect in treatment-resistant depression. The most cited article in the list (50.2 per year) also involved a psychedelic substance (psilocybin) against treatment-resistant depression, but it was just an open-label feasibility study, devoid of placebo control (Carhart-Harris et al., 2016).

The outstanding psychedelic research done in Brazil was completely unknown to me until 2017, when I almost by chance ended up attending and reporting on the Psychedelic Science conference held in Oakland. My 35-year career in science journalism until then had concentrated in issues such as genomics, climate change and Amazon deforestation, with a few incursions in neuroscience but no attention to entheogens. After seeing an announcement about the event in California, I browsed the online program and was startled to find there two Brazilian researchers that I knew and respected, Sidarta Ribeiro and Stevens Rehen. I got in touch with them, and they reassured me that the conference merited coverage by *Folha de S.Paulo*, the leading Brazilian newspaper I have worked for since 1986. They also recommended that I contact anthropologist Beatriz Labate, who was organizing the Plant Medicines track of the conference and helped me get a press badge to cover it.

Once in Oakland it became clear to me that the biomedical research in psychedelics was burgeoning, and that Brazil had a prominent place in the so-called renaissance. I started writing about the subject for the Brazilian audience, which soon developed into a book project – under the title “Psychonauts: Trips with Brazilian Psychedelic Science”, the book will be launched May 10th in Portuguese by Editora Fósforo. Noticing that there was much more to report about psychedelics than could reach the pages of the actual paper, *Folha* agreed to publish a blog, “Virada Psicodélica” (meaning “psychedelic turnaround”) where I have been posting on average twice a week since October 2020. The newspaper is quite open-minded and progressive on the issue and has defended drug reform in editorials for at least three decades now.

There is a long tradition of research with psychoactive drugs in Brazil, beginning with marijuana and ayahuasca. The brew is legal in the country, based in its ceremonial use by ayahuasca religions such as Santo Daime, União do Vegetal, and Barquinha. The group that conducted the clinical trial is led by Dráulio de Araújo in the Federal University of Rio Grande do Norte (UFRN, in Portuguese) and has its roots in the Ribeirão Preto campus of the University of São Paulo (USP), a hub for ayahuasca research. It was there, at Jaime Hallak’s lab, that Araújo had organized a pioneering brain imaging study of subjects under the influence of ayahuasca published online in 2011 (de Araujo et al., 2012).

Araújo, a neuroscientist with background in physics, works in close collaboration with biologists Sidarta Ribeiro at the UFRN’s Brain Institute and Stevens Rehen at the Federal University of Rio de Janeiro (UFRJ) and IDOR (a private research institute), as well as with psychiatrist Luís Fernando Tófoli at the State University of Campinas (UNICAMP) in São Paulo State. In 2019, the quartet circulated with 13 other colleagues a study showing LSD’s potential as a cognitive enhancer, based on behavioral experiments with rodents and proteomics screening of human brain organoids (Cini et al., (2019). Anti-inflammatory and neuroplasticity effects of ayahuasca components (DMT, harmine, harmaline) and 5-MeO-DMT also belong in the group’s research portfolio.

In comparison with ayahuasca research, ibogaine’s potential for treating addiction is somewhat incipient in Brazilian labs and university hospitals, but this is expected to change in a matter of weeks or months. Under the leadership of André Brooking Negrão, the Institute of Psychiatry at USP is ready to start recruiting patients for a randomized placebo-controlled study of the Taber-

nanthe iboga shrub’s alkaloid with 80 cocaine and crack addicts in São Paulo to test safety and efficacy (phase IIb clinical trial).

Ibogaine is a powerful psychedelic that launches subjects in a dreamlike state that can last for many hours and is said to facilitate the detoxification process of addicts, both by lessening withdrawal symptoms and giving access to the trauma roots underpinning the condition. Its anti-addiction qualities have been known since 1962, when heroin addict Howard Lotsof noticed the disappearance of such symptoms after a 30-hour trip under the influence of ibogaine (Brown et al, 2016). Lotsof himself became involved with research on the alkaloid with Kenneth

Alper (Alper et al., 1999), and treatment with the controlled compound started to spread in countries where legislation and law enforcement tolerate its use.

In Australia, New Zealand, and South Africa, for instance, ibogaine can be prescribed to treat drug dependence. A similar situation prevails in Brazil, where it is neither prohibited nor controlled, but can be imported as a non-registered medicine for personal use. After meeting Lotsof over lunch at the University of Miami in 1994, Brazilian physician Bruno Rasmussen Chaves began to treat addicts with ibogaine in 1997, and by 2020, he

had already ministered the alkaloid to more than 1500 patients. Other clinics in the country have treated hundreds of addicts, some of them following the burdensome bureaucratic process, others simply under the radar of public health authorities.

Rasmussen’s clinical experience resulted in a few scientific papers, such as the retrospective study published in 2014 showing 61% of abstinence over five months after 75 alcohol, cannabis, cocaine, and crack users were given ibogaine (Schenberg, 2014). But a full, controlled, double-blind study with placebo group on ibogaine has never been performed, as is required for any drug or treatment to get approval and become standard procedure.

Negrão, a psychiatrist who worked for five years as a researcher at the NIH in Bethesda and now heads the alcohol and drug clinic at USP’s Hospital das Clínicas, where 20 addict patients seek help on any given day, five of which chronic users of crack or cocaine. “The daily praxis of a doctor attending to crack and cocaine users is very unhappy,” he says, out of frustration with high relapse rates and the lack of effective treatments.

After being turned down by quite a few research facilities, Rasmussen landed at Negrão’s door and finally found someone willing to put his claims about ibogaine’s efficacy to test. Negrão secured approvals for a clinical trial with 80 subjects (40 females and 40 males) that will be hospitalized for 10 days each to make

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sure that they remain abstinent. The research protocol involves nine psychotherapeutic sessions: four of preparation, one experimental (ibogaine), and four of integration. The drug itself will be donated by the firm Phytostan, provider of ibogaine in Brazil, at about \$1,000 per dose, and the research team has already a batch for eight patients in stock.

This is not the only Brazilian clinical trial involving ibogaine, though. The group led by Hallak is also about to start a randomized, double-blind placebo-controlled clinical trial to investigate tolerability and efficacy of the alkaloid in the treatment of alcoholism. The principal investigator is USP's Rafael Guimarães dos Santos, who plans to recruit 12 subjects among literate adults diagnosed with alcohol use disorder and a history of at least two previous failed treatments, with drug use and/or psychotherapy. The study was ready to begin last January, but the Covid-19 pandemic has hit the city of Ribeirão Preto really hard, and recruiting has been postponed until the coronavirus scourge gets under control in the region.

According to Negrão, nobody risked a clinical trial with ibogaine to treat addiction because of the drug's bad reputation. It has, indeed, been associated with fatal cardiac problems, but the risk is deemed manageable with close monitoring in a clinical setting; such as has been the case in Rasmussen's practice and will be provided at USP's hospital. There is still some prejudice in academic circles against psychedelic science, but it has been slowly eroded by the flurry of impeccable research being published in the field.

Everything is in place to start the pioneering study that will no doubt boost Brazilian psychedelic research's reputation even higher; if it were not for the COVID-19 second and deadliest wave of infections in 2021 that left no beds available for the clinical trial. Negrão is not easily discouraged, though, and plans to resume the trial as soon as the coronavirus scourge is tamed. Ibogaine against addiction is just the beginning, he promises: "I decided to do this [psychedelic research] for the rest of my life."

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