Three-decade research development of ibogaine use for the treatment of substance-related disorders: a bibliometric analysis

Fernandes-Nascimento, Maria Helha (mariahelha@hotmail.com)  
Universidade de São Paulo, SP, Brasil  https://orcid.org/0000-0001-6402-6806

Negrão, André Brooking (abnegrao@usp.br)  
Universidade de São Paulo, SP, Brasil  https://orcid.org/0000-0002-8133-6723

Ferreira-Viana, karine  
Universidade de São Paulo, SP, Brasil  https://orcid.org/0000-0002-4386-8673

Chaves, Bruno Rasmussen  
Santa Casa de Ourinhos SP Ourinhos, São Paulo, BR  https://orcid.org/0000-0001-5447-4605

Yuan-Pang, Wang  
Universidade de São Paulo, SP, Brasil  https://orcid.org/0000-0001-7076-8312

Method Article

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Abstract

Objective

To evaluate the publications on ibogaine use for substance-related disorders treatment over the last three decades.

Method

Bibliometric analysis of publications on ibogaine for the treatment of substance-related disorders from 1991 to 2020 using VOSviewer software. We performed a Scopus database search using the terms: ibogaine, 12-methoxybogamine, endabuse, tabernanthe iboga, NIH-10567, and noribogaine. Publications related to ibogaine was compared between the three decades using the Tukey test at 95% confidence level, and the behavior period evaluated considered linear and polynomial regression models.

Results

Regression models indicated that publications dedicated to ibogaine for treating substance use disorders grew by 5.1 publications per year between 1991–2000 ($R^2 = 0.993$). The period from 2001 to 2020 showed a different expansion compared to the previous period, with fluctuations within a constant flow of publications and an increase in the volume of publications was observed until the middle of this decade ($R^2 = 0.889$). The same tendency was seen in the last decade, 2011–2020 ($R^2 = 0.949$). The US is the most prominent country.

Conclusion

The present study indicates that, despite differences and fluctuations among the decades analyzed, publications continue year by year and propose future directions for new interventions in the public health.

1 Introduction

Ibogaine (12-methoxyibogamine) is a substance extracted from the root bark of the *Tabernanthe iboga* plant. Originating from the tropical forest of Africa, ibogaine is an indole alkaloid drug, and has been used in the treatment of substance-related disorders. The term alkaloid represents the plant marker responsible for the psychoactive effect, that accidentally promoted the first anti-addictive experiment by Howard Lotsof, in 1962, in the USA, paving the way for new treatment possibilities across the.
the West, its scientific relevance is in treatments for substance-related disorders, which include cocaine, opioids, heroin, alcohol, and nicotine. There are, however, concerns about its safety and legality in some countries.  

A greater interest in ibogaine was seen in 1990, with studies with rodents and the creation of the biosynthetic analogue formula 18-methoxycoronaridine (18MC).  

Recent studies have shown scientific evidence on the efficacy of ibogaine use and its “main metabolite noribogaine (18-MC)” in several countries, in both rodents and human models, for the treatment of psychiatric disorders, especially substance-related disorders. Evidence in the literature reveals that substance-related disorders have a considerable impact worldwide and reinforces the notion that new treatment alternatives have an important role for the scientific community and are fundamental for the management of these disorders.  

Recent data indicate that 271 million people, i.e., 5.5% of the world population, aged between 15 and 64 years old, are users of some kind of illicit drug. In the last decades, there has been a considerable increase in the interest of researchers in the use of novel drugs for the treatment of substance use disorders. It is noteworthy that substance-related disorders currently are showing an increasing trend associated with the rise of anxiety and stress disorders. Actions have been developed and implemented to alleviate the losses related to the economic burden and mortality, as well as to maintain the quality of life of society.  

Traditionally, the development of therapeutic alternatives aims at reducing premature illness and preventable death. Ibogaine therapy is part of a new construct of interventions for reducing harm, especially in withdrawal symptoms, even though there are still limiting challenges for its use. From this perspective, the publications have been growing in the light of the scientific literature. These propositions also have enabled current debates on the presentation of ibogaine as a promising possibility for the treatment of substance-related disorders. However, the existing publications are restricted to specific themes, and little attention has been paid to visualizing the global landscape of the scientific production of ibogaine as a treatment for substance-related disorders.

There is no detailed investigation in the literature for a systematic understanding of the general context of the development of ibogaine for therapeutic use. Thus, our objective was to perform a bibliometric analysis of the evolution of publications on ibogaine use in substance-related disorders over the past 30 years. We aim at contributing to the academic and scientific fields, with an original study addressing the following question: How have publications on the use of ibogaine in the treatment of substance-related disorders developed in the last 30 years? Based on a co-occurrence network, our specific objective was to identify a couple of elements, namely: the types of publications; annual frequency of publications in this period; countries with the highest number of publications; most cited works; most prolific co-authors; relevant keywords in the analysis; and organizations with the highest number of publications, subjects that will compose the following sessions of this study.
2 Method

We performed a quantitative and descriptive bibliometric analysis. Bibliometric analysis is a quantitative method, which analyzes bibliographic indicators, reveals the main insights of the scientific progress of a given topic, and reveals the flow of development of the scientific field.\textsuperscript{20,21} Thus, it is an important means of mapping the advancement of a discipline.\textsuperscript{20} In addition, data statistical analysis retrieved from white literature allows researchers to identify trends in the periods studied.\textsuperscript{21} These directions reveal the main frontiers of the field (authors, countries, works).

The search was performed in the SCOPUS database (Elsevier BV Company, USA)\textsuperscript{22} on May 5, 2021; access was via the CAPES/MEC Journal portal. SCOPUS was chosen as it is the largest database of abstracts and citations available in the literature and contains comprehensive peer-reviewed scientific references, in addition to including all MEDLINE documents and being the preferred database for performing bibliometric analyses.\textsuperscript{21,23,24} The publications were exported on the day they were accessed to avoid updating the database and were transferred as a CSV file to VOSviewer,\textsuperscript{25} and in RIS format to Mendeley Reference Manager. We used only one database to avoid duplication of references in the analysis.

2.1 Inclusion and exclusion criteria

We included peer-reviewed publications published from 1991 to 2020 indexed in the Scopus database on ibogaine and substance abuse. There was no restriction on language and type of publication as a way to reduce the risk of bias, considering the wide coverage of the Scopus database. Publications outside the target period (1991–2020) were excluded; publications not related to the keywords selected in the second phase of the search, as well as publications from field-related academic web pages not indexed in Scopus and from the gray literature were also excluded.

2.2 Search data

The search strategy was performed in three phases. The first one consisted of a general search on the term ibogaine and its synonyms, using the Boolean OR operator for greater coverage. A total of 2,942 publications were retrieved with the terms: "ibogaine" OR "12-methoxyibogamine" OR "12 methoxyibogamine" OR "Endabuse" OR "tabernanthe iboga" OR "NIH-10567" OR "NIH 10567" OR "noribogaine", selected through the Medical Subject Headings (MeSH) of the National Library of Medicine.

The second phase was the limitation of the period of interest (1991–2020). The option to limit the time period is available in the database and resulted in 2,695 publications. The third phase was the application of filters of exact keywords, which was an option also available in the database. "Ibogaine" OR LIMIT-TO (EXACT KEYWORD), "Cocaine" "Addiction", "Drug Dependence", "Alcohol", "Withdrawal Syndrome", "Alcoholism", "Psychedelic Agent", "Substance-Related Disorders", "Alkaloid", "Drug Abuse", "Alkaloids", "Opiate", "Noribogaine", "Alcohol Consumption", "Substance Withdrawal Syndrome", "Indole
Alkaloid”, "Opiate Addiction”, "Cocaine Dependence”. Finally, we identified 1,223 publications to compose the portfolio of the study. Figure 1 indicates a flow chart of the sequence performed for the eligibility of the studies. Duplicated publications were resolved using Rayyan Systems.  

2.3 Data management

The retrieved publications were exported in comma-separated values (CSV) file format to the VOSviewer software for bibliometric analysis and map network construction, and to the Mendeley bibliographic reference manager software (www.mendeley.com/downloads) in Research Information Systems (RIS) file format to manage the selected references. We then used Rayyan Systems, function for screening scientific research, performing a reading of titles and abstracts in order to select publications for a full reading.

2.4 Data Analysis

Bibliometric analyses were performed using the VOSviewer program (Version 1.6.10), based on data identified in the Scopus database. VOSviewer is a tool for the construction and visualization of bibliometric maps, which are constructed based on co-occurrences within the categories of analysis (keywords, co-authors, countries, and organizations). The VOSviewer software was developed by Leiden University Center for Science and Technology, for bibliographic analysis of scientific publications and has received much attention in recent years, as it contextualizes publication metrics on specific topics.

This tool features a flexible functionality for building networks of relationships associated with scientific production, including publications, journals, researchers, research organizations, countries, and keywords. The networks consist of nodes and edges that indicate the strength of the relationship between the units represented by distance; the closer the distance, the stronger the link between the units. The networks are determined by the magnitude of the strength of the links between the units, creating clusters that are differentiated by colors. Each color represents groups of affinities and the strength of collaboration between countries, organizations, authors, and important terms building general maps. Maps are formed based on the analysis of a specific item, according to the strength of the links, which indicates the number of connections between two or more items in the network.

Interpretation of the link uses the width of each line in the cluster. The wider the line in the network, the stronger the link between the items. After analyzing the documents in VOSviewer, the grouped data were transported and organized in spreadsheets in Microsoft Excel 2016, to calculate percentages and frequency, which were used to classify document types, languages, main countries where they were published, and organizations.

We also constructed a temporal distribution graph of the number of publications over the last three decades. Statistical analysis of scientific production was performed using regression models with and without intercept to understand the behavior and interpretation in each decade of study separately. Before
using the models, normality was evaluated with the Shapiro-Wilk test on the distribution of residuals, followed by the Tukey test, to investigate differences between groups. Significance was set at \( p < 0.05 \). After that, the linear and polynomial regression model with a t-test for the significance of the parameters was used, in order to obtain the model that best describes the data set for statistical analysis.

We used R software (R Development Core Team (2021)), (https://cran.r-project.org/bin/windows/) as follows: 1- Period from 1991–2000, linear regression models with and without intercept and quadratic regression models were tested in order to understand the behavior of the data. 2- Period from 2001–2010, linear regression models, quadratic regression models with and without intercept, and cubic regression models were tested. 3- Period from 2011–2020, linear regression models with and without intercept and cubic quadratic regression models were tested. The representation of the geographic area to visualize the different borders studied was carried out using QGIS Development Software. 29

3 Results

3.1 Publication production in three decades

The search retrieved a total of 1,223 publications for this bibliometric analysis. A total of 284 of them were for the period 1991–2000. In 2001–2010 and in 2011–2020, we identified 420 and 519 references, respectively. The types and number of publications identified were: Articles 791 (65%), Reviews 293 (24%), Conference Papers 47 (4%), Book Chaps. 43 (4%), Letters 17 (1%), Notes 12 (1%), Short Surveys 11 (1%), and Editorials 8 (1%). The most commonly used language was English with 1,185 (97%) publications, followed by Spanish 8 (0.65%), Chinese 7 (0.60%), German 7 (0.60%), France 5 (0.40%), Japanese 4 (0.40%), Slovenian 3 (0.20%), Dutch 2 (0.16%), Polish 2 (0.16%), Bulgarian 1 (0.10%). The number of articles published over the last three decades is presented in Supplementary Material S1.

3.2 Statistical analysis

Based on the Shapiro-Wilk test, the data were normally distributed with homogeneous variance over the three decades. Supported by the results obtained in the variation analysis, we observed a difference between the volume of publication in the three periods with a level test of 5% probability, which we confirmed via Tukey's Test (confidence interval 95%). As seen in Table 1, 1991–2000 < 2001–2010 = 2011–2020, this result is derived from the mean values of each group.
Table 1
Test of multiple comparisons- Tukey

<table>
<thead>
<tr>
<th>Decade</th>
<th>Mean Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001–2010</td>
<td>42.00 A</td>
</tr>
<tr>
<td>2011–2020</td>
<td>51.90 A</td>
</tr>
</tbody>
</table>

Note* The means followed by the same letter do not differ from each other by the Tukey test at the 5% probability level.

In order to investigate behavior within each decade, we adjusted the linear and polynomial regression models. The models showed normality in the Shapiro-Wilk test as homogeneity of variances via analysis of the residues, with significant parameters at a 5% probability level of t-student test, and $R^2$ values higher than 88%, indicating adjustment quality of the models.

Based on the adjusted models, we can infer that between 1991 and 2000, there was an increase, on average, of 5.1 publications in each year of evaluation. Between 2001 and 2010, based on the quadratic model, there was a decrease in the volume of publications in the 3rd and 4th year and an increase around the 7th and 8th year in the same decade. In 2010-2020, the same movement can be seen, with a greater decrease in the 2nd year, and an increase in the 8th year (2018). All behaviors are shown in Fig. 2. It is worth noting that both the growth rates of 2000-2010 and 2011-2020 and their expansion periods are higher than those of 1991-2020, even with fluctuations. That being said, it is possible to affirm that, despite the linear growth in the volume of publications from 1991 to 2000, this ascendancy movement was not maintained in subsequent years, although the volume was higher.

3.4 Main countries

The analysis specifies that a total of 79 countries comprised international collaboration, in three decades. Considering the criterion of one document and one citation per country, the data reflect the overall use of ibogaine in the treatment of substance-related disorders. Fig. 3 shows the distribution of the top countries in the ranking, with a minimum of 10 publications, which resulted in a total of 23 countries composing this limit with a minimum of 49 citations, in the last 3 decades.

The United States (USA) had the highest number of publications with 660 (50%), and 28,850 citations (55%), followed by: the United Kingdom with 73 (6%), and 3,501 citations (7%); Germany 63 (5%), and 4,089 citations (8%); China 58 (4%), and 1,962 citations (4%); Italy 50 (4%), and 2,193 citations (4%); Canada 49 (4%), and 1,397 citations (3%); France 46 (3%), and 530 citations (3%); Brazil 43 (3%), and 1,142 citations (2%); Netherlands 37 (3%), and 1,260 citations (2%); Poland 32 (2%), and 867 citations (2%); India 31 (2%), and 590 citations (1%); Japan 28 (2%), and 907 citations (2%); Switzerland 24 (2%),
and 598 citations (1%); Spain 23 (2%), and 597 citations (1%); Austria 21 (2%), and 432 citations (1%); New Zealand 14 (1%), and 193 citations (0.40%); Australia 12 (1%), and 486 citations (1%); Mexico 12 (1%), and 194 citations (0.40%); Malaysia 11 (1%), and 252 citations (0.5%); Portugal 11 (1%), and 249 citations (0.5%); Slovenia 11 (1%), and 49 citations (0.1%); Sweden 11 (1%), and 571 citations (1%); and Iran 10 (1%), and 171 citations (0.3%).

3.5 Most cited publications

Supplementary Material S2 details publications with a significant number of citations, and the productivity, impact, and H-index of all publications retrieved in over 30 years. The H-index connects the number of publications to the number of citations, unifying productivity. A total of 13 publications were selected using the criterion of more than 100 citations in journals, following the chronological order of publications. These studies were observed between 1991 and 2005, revealing important authors in the field. The main investigations carried out include the effects of ibogaine on the central nervous system and its affinity in specific regions, including associations with dosages, for standardization, and their interaction with opioid binding peptides (enkephalins, endorphins, and dynorphins) tested in rodents.

In independent publications, the interaction of ibogaine with three opioid class receptors was investigated: mu (µ) activated by morphine, Kappa (k), stimulated by Ketocyclazocine, and Sigma (σ), activated by the substance SKF 10047, and its action on the decrease in withdrawal symptoms. Furthermore, we found a greater contribution of studies with ibogaine in treatments for substance-related disorders (including smoking and alcohol abuse in the second decade) and the relation of its anti-addictive property to alleviate withdrawal symptoms.

3.6 Main co-authoring network

The co-authorship analysis was performed in VOSviewer with the criteria of at least five documents per author and at least one citation. A total of 3,430 authors were identified. Only 101 of them fulfilled the above criteria and were distributed in 18 clusters, separated by colors. The cluster colors indicate affinity groups, which reveal a direct link between the authors. The authors’ next reinforces the presence of co-citations, and the size of the circles indicates the number of articles by each author in the cluster. In the co-authorship count, the weight is assigned individually to each researcher.

The co-authorship network represents the visualization of collaboration between authors, countries, and partner institutions in scientific production. It demonstrates the strength of collaboration represented by the links on the maps. It can therefore be argued that the authors visible on the map (Fig. 4) were considered to have the highest number of co-authorships in the period. The author named Glick S.D., visible in the blue cluster at the center of the map (Fig. 4), was the most prolific author of the analysis. As
part of his significant body of research on ibogaine, his publications in 1990 investigated the anti-addictive properties of ibogaine, proposing the reduction of harmful effects, both neurochemical and motor. \textsuperscript{11, 38}

In addition, Glick SD was a major contributor to the creation of the congener 18-methoxycoronaridine (18-MC),\textsuperscript{39} a synthetic iboga alkaloid, with ibogaine-like effects but no adverse reactions and with relative safety potential, as well as greater selectivity.\textsuperscript{39, 40} Surprisingly, tests on rats found the efficacy of 18-MC in abstinence from morphine, cocaine, tobacco, and alcohol, among other drugs of abuse.\textsuperscript{40, 41} Taken together, these studies comprise a vast co-authorship with several scholars indicated in the map (Fig. 4), the rank of authors include - but is not limited to: Maisonneuve IM., Szumlinski k.k., Kuehne, M.E., Rezvani A.H., Bandarage, U.K., Popik, P., Arias H. R., as well as a number of prominent co-authors on the map indicated visually by the size of the circles, namely: Mash, D.C., Ali S.F., Ron, D., Kalueff A.V., Winter J.C., Alper, K.R., who have made relevant contributions, and are clearly shown in the analysis of the co-authorship network (Fig. 4).

In addition, the co-authors also pointed out relevant data on the efficacy of ibogaine and the 18-MC response in the brain. A striking observation reported the decrease in extracellular dopamine levels in specific regions, such as the nucleus accumbens, in addition to confirming the release of serotonin found in treatments with ibogaine. This could be explained by a possible affinity of ibogaine with the 5-hydroxytryptamine (5-HT) receptor \textsuperscript{42}. This discovery has clearly contributed to the current scenario around ibogaine on the globe.

### 3.7 Main keywords

Keywords were analyzed over the three decades separately. Selection criterion was set as at least 10 occurrences, to increase the field of the results visualization on maps, divided among the aforementioned period. The analysis of the first decade, from 1991 to 2000, is composed of four clusters, with a total of 16 items. In the center of the map, the keyword “ibogaine” is the most prominent circle in the red cluster. Fig. 5A illustrates 103 occurrences, total links strength 142, and a strong connection observed by the width of the links with 14 keywords related to the main scientific issues of this decade's publications in the treatment of substance-related disorders. The total strength of the links represents the strength existing between one element and another, this is represented by the width of the links, that is, a link between the keywords. \textsuperscript{25}

The second decade, from 2001 to 2010, shows an important representation in three color clusters: green, blue, and red, totalizing 13 keywords. The terms "ibogaine", "addiction", and "cocaine" were more relevant, considering the size of the circle and the strength of the link width in cluster number one (red). Cluster number two (green) indicates an intersection of the 18-methoxycoronaridine (18-MC) congener with ibogaine and dependence on cocaine, morphine, and tobacco. In cluster three (blue), we can notice
tobacco abstinence with a link to alcohol and other treatment possibilities (Fig. 5B). The absence of noribogaine is noteworthy.

The third decade, from 2011 to 2020, shows three clusters in the colors: red, green, and blue. It corresponds to 19 keywords in the selection, mainly the term “ibogaine” in the blue cluster, with 71 occurrences. The term "addiction", cluster two (red), with 55 occurrences, showed a larger circle on the map with a significant link width between the substances: alcohol, nicotine, cocaine, drug abuse, treatment, noribogaine, and 18-methoxycoronaridine (18-MC). Cluster three (green) reveals a difference from previous decades with keywords related to the presence of similar hallucinogenic psychedelics: LSD, ayahuasca, psilocybin (Fig. 5C). Morphine is not present in any cluster and noribogaine is back in the blue cluster.

3.7 Organizations

Analysis of organizations in VOSviewer was based on the criteria of at least five documents and one citation, among 2,667 organizations, and 12 met these criteria. The country with the highest number of organizations was the USA, having 5 organizations, Table 2, with a considerable number of publications. Canada had the second-highest with two organizations.

<table>
<thead>
<tr>
<th>Organizations</th>
<th>Documents</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacology and Neuroscience, Albany Medical College, USA</td>
<td>15</td>
<td>22%</td>
</tr>
<tr>
<td>Department of Chemistry, University of Vermont, USA</td>
<td>12</td>
<td>17%</td>
</tr>
<tr>
<td>Department of Psychology, University of New Orleans, USA</td>
<td>6</td>
<td>8.7%</td>
</tr>
<tr>
<td>Department of Pharmacology and Toxicology, Buffalo, USA</td>
<td>6</td>
<td>8.7%</td>
</tr>
<tr>
<td>Department of Chemistry, Medical University of Lublin, Poland</td>
<td>5</td>
<td>7%</td>
</tr>
<tr>
<td>Department of Chemistry, University of Malaya, Kuala Lumpur, Malaysia</td>
<td>5</td>
<td>7%</td>
</tr>
<tr>
<td>Veterans Affairs Medical Center, New Orleans, USA</td>
<td>5</td>
<td>7%</td>
</tr>
<tr>
<td>Department of Psychology, Mcmaster University, Hamilton, Ont. Canada</td>
<td>5</td>
<td>7%</td>
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<tr>
<td>Department of Psychology, Wilfrid Laurier University, Waterloo, Ont. Canada</td>
<td>5</td>
<td>7%</td>
</tr>
<tr>
<td>Novartis Institutes for Biomedical Research, Switzerland</td>
<td>5</td>
<td>7%</td>
</tr>
</tbody>
</table>

4 Discussion
In this study, we performed a bibliometric analysis of the literature on ibogaine in the treatment of substance-related disorders, from 1991 to 2020. Our objective was to evaluate the publishing timeline on ibogaine in substance-related disorders. A total of 1,223 publications were identified. From the information collected in the survey, the analysis pointed to a linear growth trend in the first decade, observed through the trend line of publications (Fig. 2), followed by a continuous and persistent increase, with some fluctuations, in the following decades. Despite limitations due to lack of security, the graphs (Fig. 2) indicate that there was an upward and expressive growth in the first decade, and an average maintained in the following ones, which reflects the interest of various researchers in different regions of the globe.

Even with the shortage of funding from US federal agencies, interest in ibogaine has been maintained and this persistence may be associated with the promise of new possibilities for the treatment of substance use disorders. A potentially important factor observed by this study, in the first decade, was the advance of research predominantly in cellular/molecular models. Thus, preliminary evidence in the first decade corroborates contemporary research, and it seems natural to advance the basic knowledge about a new substance before it is subjected to clinical trials. However, this tendency remains in the third decade in search of the maturity of scientific discoveries to support the regular use of ibogaine.

Consistent literature data confirm that ibogaine is still considered an illegal substance in several countries, while in other countries, such as Brazil and Canada, its use is restricted to licensed professionals or specific health conditions. In Brazil, according to the updates of Ordinance No. 344/98, despite the fact that there is no requirement to request this compound for therapeutic purposes within the country, its importation for clinical research is governed by resolution RDC 204/2006. In addition, the National Institute on Drug Abuse (NIDA) has given significant support to its use in animal research.

While in the USA, the Food and Drug Administration (FDA) classified ibogaine as a Class 1 drug, due to its neurotoxic effects, despite the approval by the agency for its use for human trials. It is believed that most of the effects of ibogaine, considered to be hallucinogenic and neurotoxic, are related to the loss of Purkinje cells, located in the cerebellum, observed in the use of doses above 25 mg/kg. Hypothetically, recent publications state that severe episodes are usually associated with the administration of high doses. However, the lack of a safe variant of the substance and the absence of technical-scientific publications to support its commercialization as a drug continue to be an impediment to its clinical use.

On the other hand, publication points to the possibility of safe doses, an argument that has gathered scientific support and was published in *Nature* (very high impact factor = 49.962 (https://www.nature.com/nature/journal-impact)), whose co-authors have ties to USA institutions. According to our analysis, the USA has the highest number of co-authors, citations, and organizations (Table 2). Additionally, this was also observed in studies carried out in China, Palestine, and Spain, which
identified the USA with great international scientific collaboration and with the highest H index. In 2018, a study found that 51% of surveys were from the USA. This scenario contrasts with the slow scientific development in some other countries.

A key issue in the USA may be subsidies from the National Institute of Health (NIH), which supports activities related to scientific research, and new achievements for health promotion. One alternative to the lack of government funds has been the support within private institutes and non-governmental organizations (NGOs), for the exploration of other psychedelics as innovative resources in mental health, e.g. maps, Hefner Institute. Despite most clinical trials approved for the use of ibogaine have been suspended after the death of a person related to the use of ibogaine in Europe.

Another important consideration in the analysis was that many co-authors who have contributed impactful work in this context are American. Among the main contributions of these co-authors are publications of considerable international relevance on anti-addictive mechanisms of action in the withdrawal syndrome. Ibogaine was also reported to reduce substance use in rats and mice in publications during the three investigated decades, for substance-related disorders such as morphine. A meta-analysis carried out in the third decade, in the Netherlands, constituted by 27 studies, reported favorably on its use in the treatment of animal models, although with some concerns related to safety were raised.

Studies also mention the effectiveness of ibogaine in the withdrawal phase of substance use, including alcohol, cocaine, heroin, opiates, and nicotine. Surprisingly, despite the inaccuracies about the adverse effects of ibogaine, the three decades reveal consistent research, maintaining the strengthening of expectations around innovations. This was demonstrated in experimental models and in case reports with positive responses. By conjecture, the evidence also reinforces the need for patient monitoring due to the absence of studies with definitive proof of its safety.

In general, in the literature investigated, ibogaine reflects an alternative field of treatment for substance-related disorders with few efficient neuroadaptive resources. From a historical standpoint, the first decade presented ibogaine in a scientific field linked to numerous themes, exploring its effects and active noribogaine (12-hidroxibogamine). The latter is generated from the metabolism of ibogaine in the liver through an O-demethylation, a chemical reaction characterized by the elimination of a methyl group from a molecule. In addition to important physiological and neurological responses, most of these studies also pointed to the influence of dopamine (DA) in the treatment performed in rodents.

Studies analyzed the ibogaine-morphine interaction with the objectives of controlling the action of dopamine (DA) in the cortex and evaluating the effect of ibogaine on the opioid, by avoiding drug-induced DA release. One study presupposed that people who have less DA in their body are more prone to addiction. Supposedly, the addition of substances favors the release of dopamine discharge in the brain. DA acts in the reward and pleasure system and, in that sense, plays an important role in the
This mechanism happens through the dopamine transporter (DAT), which is necessary to increase extracellular levels of DA. This interaction is only possible through the action of target receptors with the Sigma-1 receiver ($\sigma_1$ R). A bibliometric analysis pointed out the relevance of the Sigma-1 receiver ($\sigma_1$ R), with a close link in the treatment of substance-related disorders. The Sigma-1 receptor is the most cited chaperone protein in the cluster of a study, as it integrates the main receptors of this action. Although studies indicated that neurotoxic effects may occur associated with substance overuse, affecting the DAT system. Nevertheless, the presence of neurotoxic and cardiotoxic effects was reinforced in publications in the first and second decades, including the occurrence of death outcomes.

Studies from the first and second decades have also made significant contributions, mainly because they revealed efficacy outcomes, despite anecdotal experiences. A positive aspect was the reduction of withdrawal symptoms, including changes in motor activity significantly. A case study with 14 participants evidenced a significant response to opioid withdrawal. A survey carried out with patients who had undergone previous treatments without success found a significant result with the use of ibogaine.

In the third decade, studies have linked the properties of ibogaine with the relief of withdrawal symptoms. Furthermore, an important aspect of the analysis (Fig. 5B and 5C) was the frequency of co-occurrence of the synthetic analog 18-methoxycoronaridine (18-MC). Effective leading keywords, in specific co-occurrence, are the literature data with the highest rise in the period. The synthetic analog 18-methoxycoronaridine (18-MC) is an anti-addictive agent, synthesized by Stanley D. Glick, Martin Kuehne, Upul Bandarage, and collaborators at the University of Vermont, Burlington, VT, tested in rodents. However, studies with synthetic 18-methoxycoronaridine (18-MC) indicated possibilities for treatments without side effects. Differently from ibogaine with reports of side effects such as involuntary tremors and bradycardia, seen at high doses. Eventually, involving the release of DA in brain regions such as the nucleus accumbens and prefrontal cortex. Ibogaine and 18-MC have similar characteristics, as both are stored in adipose tissue, due to their lipophilic property and affinity for receptors specific. According to the analysis of the third decade, research on the effectiveness of 18-MC remains in the light of the literature and expands the strength of the links in a triad between 18-MC and ibogaine, and the arrival of classic psychedelics.

Psychedelics are part of a new alternative paradigm that has advanced in recent years in the academic field, as studies support robust responses on the improvement of cognitive function and mood. Similarly to ibogaine and the 18-MC, the use of psychedelics is still restricted in most countries. This fact may be associated with the possibility of sensory-perceptual alterations and the efficacy and safety are still imprecise. Traditionally, the most common substances are lysergic acid diethylamide (LSD),
mescaline, dimethyltryptamine (DMT), psilocybin, 4-methylenedioxymethamphetamine (MDMA), and ayahuasca. 64, 68

According to a study, psychedelics are classified as serotonergic agonists by interacting through the 5-HT serotonin receptor. 6 Furthermore, they have been included in studies for the treatment of substance-related disorders in the last decade, and have been used in normal doses or microdoses. 68 – 70 Studies have brought to light the concept of microdosing as a minimal dose of a substance used therapeutically. Recent studies have also claimed that microdosing does not induce sensory-perceptive effects and may produce benefits analogous to those of conventional psychedelic therapy. 66, 71, 72

The study of Cameron et al. (2019) 73 revealed evident responses with microdosing of psychedelics to improve the energy potential of the body and a variety of physical benefits, mainly treating anxiety, depression, and substance-related disorders. 1, 71, 72 However, the research is still considered inconclusive, despite clear evidence regarding the antidepressant action of psychedelics because it is anchored in plasticity and in reorganizing the functions of brain structures. 12

There are parsimonious reports that by activating the structural and functional plasticity of synapses, psychedelics act by modifying rigid brain patterns and altering prefrontal limbic neural circuits. 1, 4, 74 Other therapeutic particularities of psychedelics involve supposed affinity with receptors such as 5HT-2A, which are ion channel proteins of ionotropic receptors. 6, 74 Thus, the studies share data that involve reports of interventions with effective responses and well-tolerated doses, although all the experiences reported in the publications have been with small samples and short investigation periods. 70, 75

A systematic review carried out in 2020 with 11 studies (RCTs) revealed a strong therapeutic potential of the use of LSD in the treatment of alcoholism. 76 In 2014, a pilot study pointed out psilocybin therapy as promising for smoking cessation compared to other therapies. 68 While another study, in the Netherlands, reported on experience with various psychedelics in qualitative studies comprising 178 patients that included LSD, ibogaine, ayahuasca, ketamine, and MDMA with a promising response. 4 Hypothetically, it is assumed that the existing limiting discriminations for new clinical trials become more flexible, given so many scientific efforts.

Pondering that the inclusion of new treatment possibilities also involves the flexibility of the existing treatment prototypes. 62, 65, 66 Ultimately, several publications have identified the therapeutic potential of ibogaine for the treatment of substance-related disorders and other mental illnesses, which has stimulated research since 1991, as also publications with new insights into this demand. 66, 68, 69 Nevertheless, there is still a need to strengthen this scientific collection with controlled double-blind clinical trials, to encourage definitive advances in science in this context.

Conclusion
In the period analyzed, despite fluctuations in the number of publications, the growth rate remained constant over the years. The USA is a major producer and its authors have made great strides in the field of ibogaine research. Current scientific conjectures state that ibogaine is an alternative neuroadaptive approach in the treatment of substance-related disorders. The development of research opens the door to the identification of new treatment frontiers and, thus, contributes to the formulation of strategies for intervention programs in the field of public health.

**Abbreviations**

18-MC  
18-metoxicoronaridine  
5-HT  
5-hydroxytryptamine  
LSD  
Lysergic acid diethylamide  
DMT  
Dimetiltriptamine  
MDMA  
4-metilenodioximetanfetamine  
EUA  
United States of America  
USA  
United States  
DA  
Dopamine  
DAT  
Dopamine transporter  
RCTs  
Randomized clinical trials  
NMDA  
N-methyl-D-aspartate receptor  
FDA  
Food and Drug Administration  
NIDA  
National Institute on Drug Abuse  
NGOs  
non-governmental organizations

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References


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Figure 4

A collaborative network of co-authors in the field of ibogaine and substance-related disorders
Figure 5


B Main keywords from 2001-2010.

C Main keywords from 2011-2020.
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