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Ethnopharmacological studies in 21st century Brazil: a systematic review

Estudos etnofarmacológicos no Brasil do século XXI: uma revisão sistemática

Estudios etnofarmacológicos en el Brasil del siglo XXI: una revisión sistemática

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Alex Sander Lopes da Silva
ORCID: https://orcid.org/0000-0002-5918-1366
Universidade do Estado da Bahia, Brazil
E-mail: sanderlopes@gmail.com.br
Maria Luiza Silveira de Carvalho
ORCID: https://orcid.org/0000-0002-6887-2062
Universidade Federal da Bahia, Brazil
E-mail: silveiradecarvalho@gmail.com
Clícia Maria de Jesus Benevides
ORCID: https://orcid.org/0000-0002-7214-1318
Universidade do Estado da Bahia, Brazil
E-mail: cbenevides@uneb.br

Abstract
Brazil is a country with a large party of the population, including traditional communities, that use plants for medicinal purposes, however, the prospect of drugs derived from plants is still little explored. The present study aimed to carry out a systematic review of the literature, in an attempt to understand how studies involving ethnopharmacology have developed in Brazil during the 21st century. The *Scielo* and *PubMed* data bases were used, using the keywords "ethnopharmacology" and "Brazil". In a total of 212 articles were selected and the highest number of publications in the years of, respectively: 2018 (9.43%), 2020 (8.96%) and 2014 (8.96%). Experimental studies (laboratory studies, such as phytochemicals and biological activity) accounted 41.98% of the total, followed by literature reviews (36.32%) and ethno-directed interviews (20.28%). The results showed that the most common types of studies were popular use and biological activity (33.96%), followed by studies of popular use, phytochemical composition and biological activity (21.70%) and ethno-directed survey (20.75%). The most cited botanical families were Fabaceae (8.49%), Asteraceae (5.19%) and Lamiaceae (2.83%) and the main biological activities evaluated were anti-inflammatory (10.85%), antimicrobial (10 .85%), antimalarial (5.19%) and antioxidant (4.72%). Among the traditional communities surveyed were rural communities (50%) and quilombola communities (13.64%). The present study indicates that there was a significant increase in publications involving ethnopharmacology in Brazil, mainly from 2010, associated with a greater diversification of the researched objectives.
Keywords: Ethnopharmacology; Ethno-directed; Medicinal plants; Brazil.

Resumo
O Brasil é um país no qual uma grande variedade de comunidades, incluindo comunidades tradicionais, utilizam plantas para fins medicinais, entretanto, a prospecção de drogas derivadas de plantas ainda é pouco explorada. O presente estudo teve como objetivo realizar uma revisão sistemática da literatura, na tentativa de compreender como os estudos envolvendo a etnofarmacologia se desenvolveram no Brasil durante o século XXI. Foram utilizadas as bases de dados *Scielo* e *PubMed*, utilizando-se as palavras-chave "etnofarmacologia" e "Brasil". Foram selecionados 212 artigos e os anos com maior número de publicações foram, respectivamente: 2018 (9,43%), 2020 (8,96%) e 2014 (8,96%). Os estudos experimentais em laboratório representaram 41,98% do total, seguidos por revisões de literatura (36,32%) e entrevistas etnodirigidas (20,28%). Os resultados mostraram que os tipos de estudos mais comuns exploraram o uso popular e a atividade biológica (33,96%), seguidos de estudos de uso popular, composição fitoquímica e atividade biológica (21,70%), seguidos das entrevistas etnodirigidas (20,75%). As famílias botânicas mais citadas foram Fabaceae (8,49%), Asteraceae (5,19%) e Lamiaceae (2,83%) e as principais atividades biológicas avaliadas foram anti-inflamatória (10,85%), antimicrobiana (10,85%), antimalárica (5,19%) e antioxidante (4,72%). Entre as comunidades tradicionais pesquisadas estavam comunidades rurais (50%) e comunidades quilombolas (13,64%). O presente estudo indica que houve um aumento significativo de publicações envolvendo etnofarmacologia no Brasil, principalmente a partir de 2010, associado a uma maior diversificação dos objetivos das pesquisas.
Palavras-chave: Etnofarmacologia; Estudos etnodirigidos; Plantas medicinais; Brasil.

Resumen
Brasil es un país en el que gran parte de la población, incluidas las comunidades tradicionales,, utilizan las plantas con fines medicinales, sin embargo, la prospección de fármacos derivados de las plantas aún es poco explorada. El

presente estudio tuvo como objetivo realizar una revisión sistemática de la literatura, en un intento de comprender cómo se desarrollaron los estudios que involucran la etnofarmacología en Brasil durante el siglo XXI. Se utilizaron las bases de datos *Scielo* y *PubMed*, utilizando las palabras clave "etnofarmacología" y "Brasil". Se seleccionaron un total de 212 artículos y los años con mayor número de publicaciones fueron, respectivamente: 2018 (9,43%), 2020 (8,96%) y 2014 (8,96%). Los estudios de laboratorio experimental representaron el 41,98% del total, seguidos de revisiones de literatura (36,32%) y entrevistas etnodirigidas (20,28%). Los resultados mostraron que los tipos de estudios más comunes exploraron uso popular y actividad biológica (33,96%), seguidos de estudios de uso popular, composición fitoquímica y actividad biológica (21,70%), seguidos de entrevistas etnodirigidas (20,75%). Las familias botánicas más citadas fueron Fabaceae (8,49 %), Asteraceae (5,19 %) y Lamiaceae (2,83 %) y las principales actividades biológicas evaluadas fueron antiinflamatoria (10,85 %), antimicrobiana (10,85 %), antipalúdica (5,19 %).) y antioxidante (4,72%). Entre las comunidades tradicionales encuestadas se encontraban comunidades rurales (50%) y comunidades quilombolas (13,64%). El presente estudio indica que hubo un aumento significativo de publicaciones sobre etnofarmacología en Brasil, principalmente a partir de 2010, asociado a una mayor diversificación de los objetivos de investigación.
Palabras clave: Etnofarmacología; Estudios etnodirigidos; Plantas medicinales; Brasil.

1. Introduction

Since antiquity, humans have used plants for medicinal purposes, this being the main practice for fighting diseases and restoring health until the mid-20th century (Barbosa *et al.*, 2012; Cardoso *et al.*, 2017; Sales *et al.*, 2015). From the improvement of techniques for the synthesis of chemical compounds, developed by the pharmaceutical industries at a more accentuated level from the 1940s onwards, synthetic substances started to occupy most of the international medicine market, due, among several factors, to the possibility large-scale production and greater control of composition and dosage (Pinto *et al.*, 2002; Fernandes, 2004; Viegas Jr. *et al.*, 2006).

Despite this, it is assumed that approximately 25% of all drug prescriptions are still formulations based on substances derived from plants, synthetic analogues or their derivatives and that the use of plants for medicinal purposes has a much higher percentage expressiveness in developing countries, in rural areas and in traditional communities (Newman & Cragg, 2007). This, due to the sociocultural background, as well as the precariousness of conventional medical care, which makes traditional medicine the only resource available to most of these populations (Cavaglier & Messeder, 2014; Sales *et al.*, 2015).

In this context, Brazil represents one of the countries with the greatest biodiversity in the world, with 49,979 native, cultivated and naturalized species (Flora do Brasil, 2020), thus having an immense potential, as yet unexplored, for the prospecting of plant-derived drugs. The prospection of bioactive plant compounds of pharmaceutical interest has taken place through different analytical methods, among which the random, ethological, chemotaxonomic or phylogenetic approaches and the ethno-directed approach stand out (Albuquerque & Hanazaki, 2006). The latter consists of the selection of species according to the indication of specific population groups, usually, but not only, traditional communities, using the application of their empirical knowledge in their health and disease systems as substrate for the expansion of scientific knowledge. This type of approach has shown expressive results how in the study conducted at Sinai (Egypt) for plants with antimicrobial activity, 83.3% of the species obtained positive results by the ethnoguided approach against 41.7% in the randomized approach (Barbosa *et al.*, 2012).

According to the National Commission for the Sustainable Development of Traditional Communities of the Ministry of Social Development of Brazil, traditional peoples and communities are defined as: "culturally differentiated groups that recognize themselves as such, who possess their own forms of social organization, which occupy and use territories and natural resources as a condition for their cultural, social, religious, ancestral and economic reproduction, using knowledge, innovations and practices generated and transmitted by tradition" (Brasil, 2007). This definition includes indigenous peoples, "quilombola", peoples of African origin or "terreiros", romani people, riverside people or "ribeirinhos", artisanal fishermen, extractive communities in general, "geraizeiros", among others (Brasil, 2007).

Many of these traditional communities, mainly in developing countries, still make extensive use of plants for medicinal purposes (Arruda *et al.*, 2019). The sustainable management of biological resources for the development of drugs, if carried out together with the maintenance of traditional knowledge and practices, respect and sociocultural valuation and with effective economic return to these communities, can help to resolve the dichotomy "economic development" versus " environmental preservation", so on the agenda nowadays, especially with regard to the Amazon biome (Ministry of the Environment, 2000).

It must be considered that, in the sociocultural and religious context of these communities, health promotion takes place through a holistic perception, in the mental, physical and spiritual dimensions, generally seen in an inseparable way (Brazil, 2018; Paz *et al.*, 2015; Arruda *et al.*, 2019). In addition to the cultural envelope, the strong empirical experience of these communities is extremely valuable for the construction of academic and scientific knowledge, however, extremely difficult without understanding the first one. As emphasized by Sales *et al.* (2015), the main purpose of ethnopharmacology is to understand the interrelationships between traditional communities and their use of medicinal plants and, for this to occur, it is necessary to fully understand the concepts of the sociocultural system from which the information is obtained, since non-contextualized observations are scientifically useless.

In this context, transferring knowledge from a specific cultural language to the scientific language without a good understanding of the two languages is an extremely difficult task and prone to several interpretative errors. An initial sociocultural immersion is necessary to enable the understanding of the information received, so that these data can be correctly translated into scientific language. Thus, understanding the sociocultural aspects and cultural identity of the traditional communities under study is extremely important (Sales *et al.* 2015; Silva *et al.* 2021).

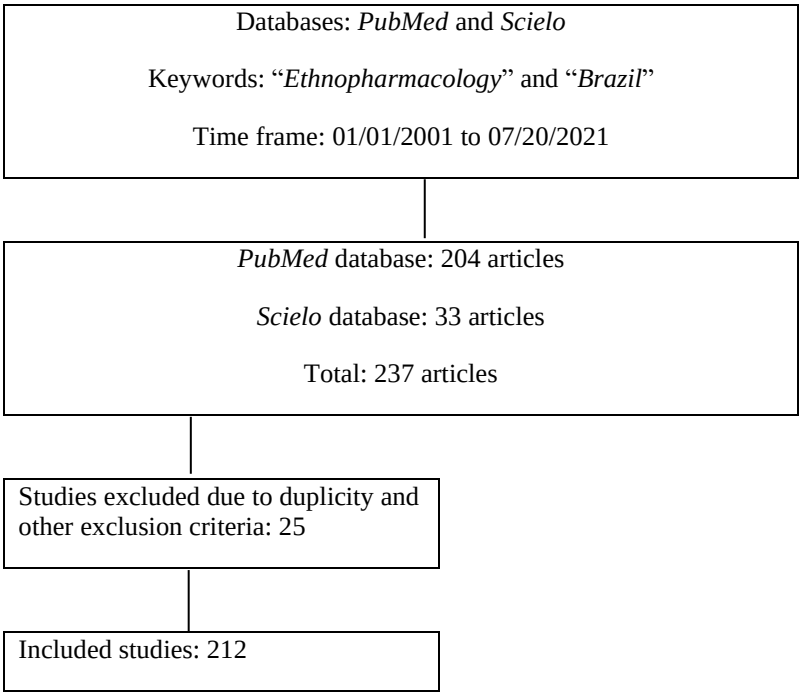
With the advance in the knowledge of the bioactivity of plant secondary metabolites, there was an increase in both ethno-directed surveys and ethnobotanical studies to identify plants used for therapeutic purposes, mainly those used by traditional communities, as well as in the number of studies on the phytochemical composition and biological activity of the substances present in the various plant species (Pagnocca & Hanasaki, 2020). The publication of the National Policy on Medicinal Plants and Herbal Medicines (PNPMF), in 2006, which encourages research with exotic, adapted or native plants, as well as the Collegiate Board Resolution (RDC) 14/2010, later replaced by RDC 16/2014, of the National Health Surveillance Agency (ANVISA), which provides for the registration of herbal medicines, created an even more favorable environment for ethnopharmacological research in Brazil, by providing clear guidelines for the manufacture of herbal medicines and for their inclusion in pharmaceutical assistance within the Unified Health System (SUS) (Sales *et al*., 2015).

In an attempt to understand how studies involving ethnopharmacology have been developed during the present century in Brazil, due to the PNPMF and resolutions of the National Health Surveillance Agency (ANVISA), the advance in knowledge of the bioactivity of vegetable secondary metabolites and the greater popularization of equipment and research techniques, the aim was to carry out a systematic review of the literature, by prospecting scientific articles in specific databases.

2. Methodology

The systematic review of literature was carried out in databases such as *Scielo* and *PubMed*, using the keywords "ethnopharmacology" and "Brazil". The time frame covered the years 2001 to July 20, 2021, with the aim of portraying only the works published in the present century (Figure 1).

Figure 1. Quantitative representation of the systematic literature review.



Source: adapted from the PRISMA flowchart. Prepared by the Authors.

In order to identify how ethno-directed research has been developed within the national reality in recent years and whether it is possible to correlate the development of specific public policies with the quantity and profile of academic research related to them, were defined as inclusion criteria: articles that described an ethnopharmacological survey, chemical composition tests, biological activity tests or toxicity tests and studies with the association of one or more of these objectives, related to medicinal plants used by traditional communities, carried out by researchers from Brazilian institutions or those in partnership with researchers from foreign institutions, written in English or Portuguese. As exclusion criteria, we used publications that did not address the chosen topics, publications duplicated by the search system or keywords used for the research that appeared only in the discussion of the article, without presenting great relevance and contextualization of the topic.

The articles that met the inclusion criteria were tabulated for descriptive statistical analysis, performed using the Stata® software (Sousa and Silva, 2000). In order to better understand the results and establish a method for performing the descriptive statistical analysis, the selected articles were separated into groups that showed differences between the variables, such as: types of study (literature review, field interviews, experimental studies in the laboratory, comparative study between ethno-directed and random collection method) and purpose or objective of the study (identification of the phytochemical composition, verification of biological activity in vitro or in vivo, toxicity verification, survey of popular use through semi-structured interviews, among others).

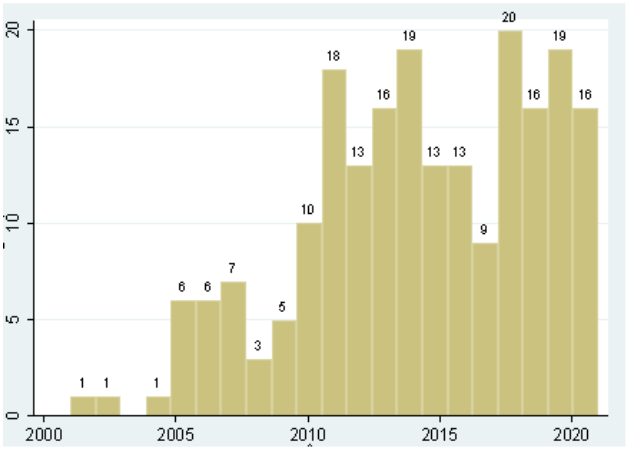
3. Results and Discussion

3.1 Profile of selected articles and quantitative by year of publication

Were found 237 articles, of which 212 were relevant to the inclusion and exclusion criteria. Of the works analyzed, 91.04% were developed by researchers in national institutions and 8.96% by Brazilian researchers in partnership with foreign institutions (Figure 2). No foreign researches were found in national territory without partnerships with researchers or national

institutions, probably due to the restriction of access via authorizations to the genetic heritage and associated traditional knowledge and remittance abroad, for the cases referred to in art. 13 of Law No. 13,123 of 2015 (Brazil, 2016).

Figure 2. Number of articles that met the inclusion and exclusion criteria (y axis) versus year of publication (x axis).



Source: Authors.

Considering the year of publication/percentage of articles published ratio, those with the highest publication were: 2018 (9.43%), 2020 (8.96%) and 2014 (8.96%), with a significant increase in publication of articles with an ethnopharmacological focus in the second decade of the 21st century (Figure 2). This substantial growth may be associated, among other factors, with the publication of the PNPMF and ANVISA's resolutions, in order to regulate and support the criteria for releasing the commercialization of herbal medicines, as one of the main guidelines of this policy is precisely to promote the encouragement of research and development of medicinal and herbal plants, prioritizing the country's biodiversity (Brazil, 2006).

The results found also indicate that the increase in the number of publications of articles started in 2005 (Figure 2), a year of great mobilization for the construction of the text that would make up the PNPMF, jumping from one article/year to six/year, maintaining it became like that in 2006 and rising to seven in 2007. On the other hand, the number of articles published fell in 2008 and 2009, again doubling in 2010, the year after which the number of articles published/year no longer returned to levels lower than the publication of the PNPMF (year 2006, with six articles published).

Some hypotheses for the fall in publications in the years 2008 and 2009 were the global economic crisis and the delay in the publication of resolutions that would regulate this policy, by ANVISA. In this regard, the impact of ANVISA's Collegiate Board Resolution (RDC) 14/2010, later replaced by RDC 16/2014, which provides for the registration of herbal medicines and which defined clear regulations on how the PNPMF would affect the productive sector regarding parameters required for proof of efficacy and safety. In this resolution, it was defined that the efficacy and safety of herbal products must be established through one of the following options: punctuation in technical-scientific literature (referenced in ANVISA's Normative Instruction 05/2010); preclinical and clinical trials of safety and efficacy; proof of traditional use or presence in the "List of herbal medicines for simplified registration", published by ANVISA in Normative Instruction No. 5, of December 11, 2008, or its updates (Brazil, 2014). Therefore, the significant increase in publications from 2010 onwards may be associated with this definition of clear rules, which guided what was expected for the study of medicinal plants and herbal medicines.

With regard to the relevance of publications, 48.58% of the articles were published in an impact factor journal (IF) 4.360, 6.60% (IF 1.754), 3.30% (IF 2.629), 2.36% (IF 4.411), 1.89% (IF 1.266), 1.89% (IF 3.503) and 1.89% (IF 4.087), indicating the highest international relevance of the published articles.

To analyze the "type of study" published, publications were categorized into different groups, such as: literature review, laboratory experimental studies, field research with ethno-directed interviews, among others, according the Table 1. Experimental studies corresponded to 41.98% (89), followed by literature reviews (36.32% or 77), ethno-directed interviews (20.28% or 43), studies with association of ethno-directed interviews with experiments (0 .94% or 2) and a comparative study between the results obtained with an ethno-directed study versus random collection (0.47% or 1). Most literature reviews aimed at compiling and associating data from various studies on the same plant species, or set of species, bringing its popular use by traditional communities and associating it with studies of phytochemical composition and biological activity, providing an integralist view of scientific data obtained by previous research, such as the study by Sá and Elisabetsky (2012), who portrayed the development of traditional medical systems in Brazil and by Paim *et al.* (2020), who discussed 39 species of Connaraceae with pharmacological potential.

Table 1. Analysis of national and international articles based on inclusion and exclusion criteria according to the classification created for the variable “type of study”.

Year	Literature Review	Ethno-directed Interviews	Experimental studies	Ethno-directed Interviews with Experimental Studies	Comparative study “ethno-directed *versus* random selection”	Total
2001	1	0	0	0	0	1
2002	0	1	0	0	0	1
2004	0	0	1	0	0	1
2005	1	2	3	0	0	6
2006	0	4	2	0	0	6
2007	5	2	0	0	0	7
2008	1	0	2	0	0	3
2009	0	3	2	0	0	5
2010	3	5	2	0	0	10
2011	5	4	9	0	0	18
2012	4	3	6	0	0	13
2013	4	1	11	0	0	16
2014	3	5	10	1	0	19
2015	3	6	4	0	0	13
2016	6	2	5	0	0	13
2017	3	1	5	0	0	9
2018	11	2	7	0	0	20
2019	7	1	7	0	1	16
2020	9	1	8	1	0	19
2021	11	0	5	0	0	16
Total	77	43	89	2	1	212

Source: Authors.

In order to better understand the objectives of the articles, the "purpose" of the articles was created and analyzed, as an example of verification of biological activity, phytochemical composition, toxicological profile, among others and their associations (Table 2). This aimed to distinguish, for example, whether an experimental study was exclusively for phytochemical composition, biological activity, ethno-directed field research, or whether the study made an association of these purposes.

Table 2. Analysis of national and international articles based on inclusion and exclusion criteria according to the "purpose", associated with the objectives of the work. Frequency refers to the absolute quantitative.

Study Description	Frequency	Percentage
1. Popular use and biological activity	72	33.96
2. Popular use, phytochemical composition and biological activity	46	21.70
3. Ethno-directed survey studies	44	20.75
4. Popular use, phytochemical composition, biological activity and toxicology	15	7.08
5. Phytochemical composition and biological activity	14	6.60
6. Toxicological analysis	5	2.36
7. Popular usage and taxonomic relationship	2	0.94
8. Popular use and phytochemical composition	3	1.42
9. Biological and toxicological activity	3	1.42
10. Phytochemical composition and toxicological analysis	1	0.47
11. Ethno-directed survey and biological activity	1	0.47
12. Biopiracy, patents and return to traditional communities	1	0.47
13. Botanical identification and popular names	1	0.47
14. Biological activity and *in silico* assay	1	0.47
15. Genetic composition and variability	1	0.47
16. Adverse reactions	1	0.47
17. Random and comparative collection with popular usage	1	0.47

Source: Authors.

The results found showed that the most common types of study were: studies of popular use and biological activity (33.96%), followed by studies of popular use, phytochemical composition and biological activity (21.70%) and ethno-directed survey (20.75%) through field interviews. It is observed that most of the articles had more than one objective/purpose, however, they aimed to understand and establish a relationship between the plant drug and a pharmacological effect, as well as to elucidate which phytochemical components present in plants are responsible for promoting the pharmacological action traditionally reported, like the study by Salehi *et al.* (2020), who verified the antimicrobial, antioxidant and anticancer effects of plants of the Anacardium L. genus.

These studies are very important, as they promote the development of one of the PNPMF guidelines, which is to identify and implement mechanisms for validation and recognition of the use of plants for medicinal purposes, which take into account the different systems of knowledge, associating traditional knowledge to technical and scientific knowledge. This association of knowledge is essential for collecting data that corroborate the efficacy and safety of the use of herbal medicines developed from a plant species, according to RDC 16/2014, as well as for the inclusion of the medicinal plant in the National List of Plants Medicinal and Herbal Medicines of the National List of Essential Medicines (RENAME-FITO), base list for the supply of medicinal plants and herbal medicines to users of the Unified Health System (SUS) (Brazil, 2006).

3.2 Ethno-directed survey studies

The ethno-directed survey studies (Table 2, item 3), carried out through semi-structured interviews, corresponded to 20.75% of the analyzed articles. These studies are essential for initial prospecting, which serves as a guide for future research on phytochemical composition, biological activity or clinical research, as well as, according to RDC 16/2014, can serve as proof of its use by traditional peoples. These are one of the pillars of the analysis of efficacy and safety, in addition to corroborating the association of traditional knowledge with technical and scientific knowledge, which is so necessary for the

validation and recognition of the use of plants for medicinal purposes in the context of the PNPMF (Brazil, 2014).

The main target populations of the prospected articles, with the objective of the ethnopharmacological survey, were rural communities (50%), within which several different traditional groups are inserted, such as extractive communities, "caiçaras", rubber tappers, chestnut trees and "geraizeiros"; "quilombola communities" (13.64%); populations from large urban centers (11.36%); indigenous communities (6.82%); populations involved in popular trade fairs for medicinal plants (6.82%) and riverside communities or "ribeirinhos" (4.55%).

The choice for rural communities can be explained by the fact that these populations have between 80 and 100% more knowledge and practice with traditional medicine compared to populations in large urban centers (Bieski, 2005; Santos, 2009; Bieski *et al.*, 2012) and, in many cases, the studies do not specify the type of rural community surveyed (if extractivists, chestnut trees, "geraizeiros", etc.). Added to this fact is the likely greater lack of access to public health services and low purchasing power, which hinders access to industrialized medicines, making traditional medicine, passed on orally between generations, the main access to health treatments for part of the residents of these communities (Cavaglier & Messeder, 2014; Sales *et al*., 2015). Quilombola communities, as well as other communities with an African matrix, such as terreiro people, have a peculiar relationship with medicinal plants (Brazil, 2018). While, for some traditional communities, the purely medicinal purpose of the plants has all its cultural meaning, for the "terreiro" peoples, the plants are sacred, containing in them the "axé" or strength of the Orixás (Camargo, 2014; Brazil, 2018, Arruda *et al*., 2019). This sacralizing appeal, associated with the enhancement and preservation of ancestral knowledge, makes these communities a stronghold of rich traditional knowledge (Arruda *et al*., 2019). Added to this is the fact that most of these communities are also in rural areas, with rich natural resources that are associated with their cultural reproduction (Ministry of the Environment, 2000; Brazil, 2018; Fernandes *et al*., 2020).

According to the literature, the use of plants for medicinal purposes in indigenous communities is also notorious (Ministry of the Environment, 2000). Those communities are large holders of traditional systems of medicine that can vary enormously in their sociocultural theoretical concepts regarding the use of these plants (Morais *et al*., 2005; Tirloni *et al*., 2011; Ferreira, 2012; Kffuri *et al*., 2016). As these communities hold important traditional knowledge, a high number of publications involving these communities is likely. However, based on the survey presented here, ethnopharmacological surveys in indigenous communities represented only 6.82% of the total publications analyzed. Among several issues that may be involved in this low percentage, we highlight the delay in bureaucratic negotiations to allow the researcher to enter these lands which, despite being extremely important, lack speed. Among the various bureaucratic processes that must be followed are the authorization of the Research Ethics Committee, as this is research involving human beings (CNS, 2012); authorization of access to indigenous lands by the National Indian Foundation (FUNAI, 1995); strict compliance with Law 13,123 of May 20, 2015, which provides for access to genetic heritage, protection and access to associated traditional knowledge and on the sharing of benefits for the conservation and sustainable use of biodiversity (Brazil, 2015), with protocols through the National System for the Management of Genetic Heritage and Associated Traditional Knowledge (Sisgen, 2017) and authorizations for the collection and transport of biological material from the Chico Mendes Institute for Biodiversity Conservation (ICMBio) (ICMBio, 2015).

Studies involving people related to popular trade fairs for medicinal plants, such as herbalists, healers and consumers, accounted for 6.82% of the total number of ethnopharmacological articles with field research. This relatively low index is possibly related to the lack of credibility in terms of traditional knowledge regarding therapeutic purposes and the way in which medicinal plants are prepared by the people who sell them (Fraxe *et al*., 2007). However, these traders can serve as a source of study on some medicinal information on herbs, as well as on the hygienic-sanitary conditions of the popular trade in these vegetables (Neto *et al*., 2010).

Studies involving riverside communities accounted for 4.55% of the total ethnopharmacological field research. Although this index is also considered low when compared to the others, and its dispersion is suggested as the main cause, these traditional communities, for the most part, live in the floodplains of the Amazon biome and are holders of vast knowledge regarding the use of medicinal plants, a practice widely referred to in the region as an alternative to the treatment of numerous illnesses (Marques *et al*., 2020). As the work of doctors and other health agents specialized in these communities is rare, especially in the most isolated places, the traditional populations of the Amazon maintain in traditional medicine and in the use of plants for medicinal purposes the treatment and prophylaxis for various diseases (Fraxe *et al*., 2007).

3.3 Botanical identification and phytochemical composition

According to the results found in the survey, few botanical families were found as representative in the articles, focusing on a single species or genus (Table 3).

Table 3. Most cited botanical families in the analyzed articles (Frequency refers to the absolute quantitative).

Family	Frequency	Percentage
Fabaceae	18	8.49
Asteraceae	11	5.19
Lamiaceae	6	2.83
Anacardiaceae	5	2.36
Euphorbiaceae	5	2.36
Apocynaceae	4	1.89
Myrtaceae	4	1.89
Verbenaceae	4	1.89
Rubiacea	4	1.89

Source: Authors.

These results are in agreement with ethnobotanical surveys conducted in other tropical regions, who found the same families as more representative (Lewis, 2005; Pilla *et al*., 2006). Souza *et al.* (2014), for example, carried out a study in the region of Carrasco, Ceará (Northeast Brazil), finding as the most representative families Fabaceae (9.52%), Lamiaceae (8.57%), Asteraceae (6.67%) and Euphorbiaceae (5.71%), while Oliveira et al. (2011) in a study carried out in the Pantanal region of Mato Grosso (Center-West), found Fabaceae (10.2%), Asteraceae (7.82%) and Lamiaceae (4.89%). Romanus et al. (2018), in its turn, evaluated the use of medicinal plants used by northeastern migrants in the State of São Paulo (Southeast Brazil) and found as the most representative families Lamiaceae (10.69%), Asteraceae and Fabaceae (9.92% each) and Euphorbiaceae (8.40%). All these studies show that the three families widely used for medicinal purposes in different regions of Brazil are Fabaceae, Asteraceae and Lamiaceae, even with percentage changes and relevant positioning among themselves. These data are in accordance with the diversity of these same families, which represent very diverse groups (Stevens, 2001 and constantly updated), including the Brazilian flora, with approximately 3,025, 2,205 and 589 species, respectively (Flora do Brasil 2020). It is also interesting to note that Fabaceae, Asteraceae and Lamiaceae constitute the most diverse families of angiosperm plants (Soltis et al. 2005) that have high secondary metabolism and, therefore, it is expected that they contain a significant concentration of bioactive compounds associated with activities therapeutic and, therefore, extensively studied.

The focus of use on species from similar families showed that phylogenetically close plants (with a high degree of relatedness) used for the same purposes have utilitarian equivalence, that is, they are more likely to have similarities (including chemical) to each other (Reinaldo et al. 2020). In this sense, Reinaldo et al. (2020), demonstrated, in his study, the influence of

kinship between groups of plants in the selection of medicinal species among peoples from the semiarid and humid regions of Northeastern Brazil. Although this type of study is still little explored (representing only 0.94% of the articles analyzed), the results seem promising and point to the need for more in-depth investigations, mainly because they indicate that plant identification permeates academic concepts and has a own perspective within the context of traditional knowledge from different communities, with its own botanical identification methods (Reinaldo et al. 2020).

Regarding the studies involving phytochemical analysis with identification of the substances that make up the extracts, they represented 36.8% of the articles analyzed here, taking into account the works where there was an association of this type of analysis with other parameters, such as biological activity and toxicological. Probably, the popularization of equipment and techniques for isolation and identification of substances, such as high-performance liquid chromatography (Maldaner & Jardim, 2009), has a great influence on these data, as well as phylogenetic studies (Soltis *et al.*, 2005).

However, it is important to emphasize that the phytochemical composition can vary according to seasonality, circadian rhythm and phase of plant development, in addition to environmental factors such as temperature, water and nutrient availability, amount of exposure to ultraviolet radiation, altitude, attacks of pathogens, among others (Gobbo-Neto and Lopes 2007), These variations can change the pharmacological response in the dose of the pharmacologically active component in plant drugs and, therefore, the quali-quantitative study of the phytochemical composition of plant drugs, extracts or herbal medicines used in biological activity tests is essential for understanding causality (Cardoso *et al*., 2017).

3.4 Biological activity studies of plants of recognized popular use

Works involving assays of biological activity of plants of recognized popular use (item 1 of Table 2) or fractions of extracts or isolated compounds from them, or even reviews containing this theme, were the most published in Brazil during the 21st century, in which it concerns ethnopharmacology, representing 33.96%, according to the results found in the present study. If considering studies involving the analysis of biological activity associated with other parameters (items 1, 2, 4, 5, 9, 11 and 14 of Table 2), such as toxicological analysis (items 4 and 9 of Table 2) and phytochemical composition (items 2, 4 and 5 of Table 2), this index is 71.70%.

The classification of articles considering the variable "main pharmacological effect" is shown in Table 4.

Table 4. Articles based on inclusion and exclusion criteria considering the "main pharmacological effect" of the reported biological activity. Frequency refers to the absolute quantitative.

Main pharmacological effect	Frequency	Percentage
Anti-inflammatory	23	10.85
Antimicrobial	23	10.85
Antimalarial	11	5.19
Antioxidant	10	4.72
Antihypertensiv	9	4.25
Gastroprotetor	8	3.77
Antidiabetic	8	3.77
Neurological and psychiatric disorders	6	2.83
Antitumor	6	2.83
Antiparasitic	5	2.36
Cardioprotective	5	2.36
Leishmanicide	4	1.89
Psychoactive	4	1.89
Antinociceptive	4	1.89
Healing	3	1.42
Antirheumatic	3	1.42
Snake bite tratament	3	1.42
Slimming	2	0.94
Oral health care	2	0.94
Sexual stimulant	2	0.94
Covid-19 tratament	2	0.94
Antidepressant	2	0.94

Source: Authors.

The main biological activities or main pharmacological effects reported were: anti-inflammatory (10.85%), antimicrobial (10.85%), antimalarial (5.19%), antioxidant (4.72%), antihypertensive (4.25%), antidiabetic (3.77%), gastroprotective (3.77%), antitumor (2.83%) and neurological and psychiatric disorders (2.83%). Among the several plants that were evaluated for their anti-inflammatory activity, Poikilacanthus glandulosus (Nees) Ariza (de Brumm *et al*., 2016), Persea cordata Meisn (Schlemper *et al.*, 2013), Macrosiphonia longiflora (Desf.) Müll.Arg. (da Silva *et al*., 2014), Ocotea odorifera (Vell.) Rohwer (de Alcântara *et al*., 2021), Garcinia brasiliensis Mart. (Santa-Cecília *et al*., 2011) and, among those that had evaluated the effect antimicrobial, we can mention Hymenaea cangaceira R.B. Pinto, Mansano & A.M.G. Azevedo (Oliveira de Veras *et al.*, 2020), Caesalpinia ferrea (Mart. ex Tul.) L.P. Queiroz (Macêdo *et al*., 2020) and Lippia L. (Oliveira *et al*., 2006).

Given the current scenario of increasing microbial resistance to classic industrialized antibiotics, research into new antibiotics is of fundamental importance and ethnopharmacology can help in the development, or rediscovery, of new therapeutic approaches based on the synergism of phytochemical compounds, as discussed by Furner-Pardoe and collaborators (2020). According to these authors, the exploration of therapeutic approaches that are not based only on individual compounds, but on a mixture of natural compounds, can result in drugs with potent antimicrobial activity, as established in their study on the anti-biofilm activity of Bald's eye drops (Furner-Pardoe *et al*., 2020).

Ethnopharmacological studies can also contribute to the establishment of therapies for diseases neglected by the pharmaceutical industry and to expand health care in regions where the local health system is deficient (Veiga & Scudeller, 2015). Veiga and Scudeller (2015), for example, studied the use of sixteen species of medicinal plants widely used in the treatment of malaria and associated diseases in the Amazon region. On the other hand, the use of medicinal plants and herbal medicines for the treatment of other neglected diseases, such as leishmaniasis and parasitosis, has been recognized and

encouraged by the World Health Organization (WHO) (Silva *et al*., 2018).

In addition to neglected diseases, the incorporation of medicinal and herbal plants in health systems, as has been happening in the SUS in Brazil, since the publication of the PNPMF, prioritizing national biodiversity, expands the therapeutic arsenal also for the treatment of everyday diseases, such as inflammation, light infections and injuries, strengthening the health system, as well as the possibilities of using resources associated with biodiversity conservation (Sales *et al*., 2015).

Consistent feedback from ethnopharmacological studies to traditional communities involves helping to create a therapeutic approach that includes the safe and rational use of medicinal plants within public health systems (Pedroso *et al*., 2021). For this to occur, it is extremely necessary to integrate traditional knowledge and technical-scientific knowledge to prove the biological activity, which guarantees the pharmacological effect, in addition to toxicity and safety studies, drug interactions and contraindications. In addition, this integration of knowledge and partnership of health systems with traditional peoples is extremely useful for promoting productive methods, such as community gardens, capable of providing medicinal plants that will be used by the public health system (Pedroso *et al*., 2021).

4. Final Considerations

The present study indicates that there was a significant increase in publications involving ethnopharmacology in Brazil, especially from 2010, associated with a greater diversification of the objectives in these works (Table 1). Experimental studies were the most numerous, especially experiments to assess biological activity and phytochemical composition of popularly used plants, followed by ethnopharmacological field research, through semi-structured interviews, which took place mainly in rural and "quilombola" communities. The main families of plants used for medicinal purposes were Fabaceae, Asteraceae and Lamiaceae, which are rich in the Brazilian flora and whose pharmacological effects were most analyzed were anti-inflammatory and antimicrobial.

Despite clear advances, ethnopharmacological studies in Brazil still have enormous potential for growth and diversification, both in relation to the traditional communities addressed, and in relation to the proposed objectives, highlighting toxicological and clinical trials, which are still little explored. Furthermore, mechanisms for returning to communities holding the researched traditional knowledge are still incipient, with little or no socioeconomic impact. The improvement of returns, in this sense, could promote awareness of sustainable development, in which traditional knowledge and the environment can be preserved not only for their intrinsic value, but also because they are a source of income and a better quality of life.

However, it is understood that the results found here present an outline of ethnopharmacological research in Brazil and not its entirety, being, however, a first step towards understanding the ethno-directed studies conducted in the country during this century. We recommend new systematic reviews, with expansion of keywords and databases, in addition to meta-analysis, in order to provide a more in-depth view of the development of ethnopharmacology in Brazil in the present century.

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