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Revisión / Review

Antibacterial activity of medicinal plants against *Leptospira* spp.: a literature review

[Actividad antibacteriana de plantas medicinales contra *Leptospira* spp.: Una revisión de la literatura]

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Section Review

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Abstract: Leptospirosis is a zoonosis caused by bacteria of the genus *Leptospira* that affects animals and humans. This disease is usually treated empirically due to its prevalence in precarious areas without basic sanitation. The use of medicinal plants in less industrialized societies has been one of the main therapeutic resources available. Considering the need to use these natural resources to combat leptospirosis in areas of socioeconomic vulnerability, this study aimed to review the literature on the use of plants with medicinal potential in the treatment of leptospirosis. The results showed that even though leptospirosis is a common disease in communities lacking basic sanitation and economic development, the number of studies on the use of plants with medicinal potential is scarce. Most of these studies come from India, and all plants investigated between 2012 and 2020 had antileptospiral action.

Keywords: *Leptospira* spp.; Medicinal Plants; Antibacterial Activity; Zoonosis; Public Health.

Resumen: La leptospirosis es una zoonosis causada por bacterias del género Leptospira que afecta a animales y humanos. Esta enfermedad suele ser tratada empíricamente debido a su prevalencia en zonas precarias sin saneamiento básico. El uso de plantas medicinales en las sociedades menos industrializadas ha sido uno de los principales recursos terapéuticos disponibles. Considerando la necesidad de utilizar estos recursos naturales para combatir la leptospirosis en áreas de vulnerabilidad socioeconómica, este estudio tuvo como objetivo revisar la literatura sobre el uso de plantas con potencial medicinal en el tratamiento de la leptospirosis. Los resultados mostraron que a pesar de que la leptospirosis es una enfermedad común en comunidades que carecen de saneamiento básico y desarrollo económico, el número de estudios sobre el uso de plantas con potencial medicinal es escaso. La mayoría de estos estudios provienen de India, y todas las plantas investigadas entre 2012 y 2020 tuvieron acción antileptospirales.

Palabras clave: *Leptospira* spp.; Plantas medicinales; Actividad antibacterial; Zoonosis; Salud pública.

INTRODUCTION

Leptospirosis is a neglected emerging zoonosis, widespread worldwide and with a major impact on public health, occurring mainly in poor and underdeveloped countries, such as the population of urban settlements (slums) and small subsistence farm workers (Torgerson *et al*., 2015). It is a disease caused by pathogenic serovars of the genus *Leptospira*, with a variety of animal hosts such as swine, canines, bovines and rodents, which keeps the bacteria in the environment and infecting new susceptible hosts, including humans (Adler, 2015).

Although many animal species, domestic or wild, can act as hosts, *Rattus norvegicus* is the main reservoir of this bacteria in the urban area, being a source of infection for the human species. Its presence in environments characterized by inadequate sanitation and poor housing contributes to increase the risk of exposure of the population to these rodent reservoirs (Naing *et al*., 2019).

Transmission occurs mainly through direct or indirect exposure to the pathogenic leptospires present in the urine of host animals that keep the pathogen in their renal tubules (Adler, 2015). The severity and/or lethality of the disease is variable according to the involvement of affected organs and the infective serovar, but commonly involves renal and hepatic failure, the main characteristics of disease of Weil (Haake & Levett, 2015).

The infection is endemic, mostly in tropical regions, with higher incidence in periods of heavy rainfall and urban flooding caused by climate variations and increased construction of impermeable areas. The release of pathogens by the urine of hosts, associated with vulnerabilities in urban risk areas, is the main route of contact with the human species (Suriya & Mudgal, 2012).

According to prospective health studies, most leptospiral infections in humans that occur in endemic areas are mild or asymptomatic, and may vary depending on the results of the association of three factors: epidemiological conditions, host susceptibility, and pathogen virulence (Haake & Levett, 2015; Jorge *et al*., 2017; Picardeau, 2017).

This association of factors results in a considerably harmful effect of the bacterial load and in a consequently higher risk to human health (Allan *et al*., 2015; Mwachui *et al*., 2015; Torgerson *et al*., 2015). More than 1 million severe cases of leptospirosis occur, with about 60,000 deaths annually, a value higher then dengue, a tropical infectious disease with similar characteristics (Costa *et al*., 2015; Picardeau, 2017).

Since it is a disease with higher prevalence in areas without basic sanitation or with few available financial resources, regional plants, whose cultural knowledge may help fight against this pathology (Punnam Chander *et al*., 2015), usually treat leptospirosis empirically.

Medicinal plants can be used in the development of pharmacopeic, non-pharmacopeic or synthetic drugs. Furthermore, these plants play a critical role in the development of human cultures around the world. Some plants are an important source of nutrition and are therefore recommended for their therapeutic values (Shakya, 2016; Ahn, 2017; van Wyk & Wink, 2018).

Today, herbal medicines are natural compounds that have properties related to medicinal activities and are accepted and practiced by people around the world. However, there are three global standards when studying the development of natural herbal medicines: the regulatory processes of each country, the scientific validation of the efficacy of botanical compounds, and the safety and efficacy of their use (Ahn, 2017).

Following the recommendations proposed by the World Health Organization (WHO) on the use of medicinal plants in public health policies, the Brazilian government created an official list of medicinal plants considered of interest for the Brazilian Unified Health System (SUS). This list, named RENISUS, describes some species with therapeutic potential for the treatment of several diseases (Giraldi *et al*., 2016).

Although Brazil is a country rich in biodiversity and availability of plants with pharmacological potential for the treatment of many pathologies, studies and scientific data on the efficacy of herbal antimicrobials or natural pharmaceutical products with inhibitory action on leptospires are lacking. Therefore, this review investigated the potential of scientifically proven medicinal plants in the treatment of leptospirosis.

MATERIALS AND METHODS

This descriptive study is a literature review aiming to synthesize the existing scientific knowledge about the use of medicinal plants in the treatment of leptospirosis. The research consisted of articles and books selected according to the inclusion and exclusion criteria. The electronic databases used were PubMed, Capes Periodicals and Google Scholar. Scientific articles were searched in Portuguese, English and Spanish, with publication data between 2012 and 2020. This period was selected to address the most recent studies on the antimicrobial action of medicinal plants in combating *Leptospira* spp. Studies published before 2012 were excluded.

The inclusion criteria were papers with a topic covering the use of medicinal plants and the pathology of leptospirosis, as well as the use of natural and/or synthetic drugs with antibacterial activity against *Leptospira* spp. The database searches performed used the keywords (isolated or combined "Leptospirosis", "Medicinal Plants", "*Leptospira* spp", and "Leptospirosis in humans."

After a systematic search and critical reading of articles and books, the selected ones were only those that met all the inclusion criteria essential for the development of this article. After, this study carried a scientifically based analysis and discussion on the data collected.

RESULTS AND DISCUSSION

Etiological agent

Although literature describes more than 260 serovars, all members of the genus *Leptospira* present a similar morphology. The leptospires are thin spiral-shaped microorganisms with approximately 6 to 20 μm in length and 0.15 μm in diameter. They usually have hook-shaped ends and two axial filaments (periplasmic flagella) that facilitate their motility. These morphological characteristics are responsible for the difficulty in visualizing fresh, with the dark field microscope being one of the most effective instruments for their observation (Schuller *et al*., 2015; Yamaguchi *et al*., 2018; Karpagam & Ganesh, 2020).

The composition of their cell structure is similar to Gram-negative microorganisms with an envelope consisting of a cytoplasmic membrane, a periplasmic space, an internal membrane and a protoplasmic cylinder (Adler, 2015). The external membrane of spirochetes has few transmembrane proteins; lipopolysaccharide molecules (LPS), important in the distinction of serovars; and large amount of lipoproteins such as LipL32, LipL41, and Ligs, responsible for the adhesion of leptospires into host tissues and for resistance of the complement system (Fraga *et al*., 2016). As with most other Gram-negative bacteria, the variation in carbohydrate composition of the LPS reflects the diversity and amount of serovars present in the genus (Adler, 2015).

Consequently, immunity is serovar-specific and therefore current animal vaccines are composed of various serovars according to the epidemiology of each region (Ellis, 2015). An unusual feature of leptospiral LPS is the activation of host cells via TLR2 instead of TLR4. This factor is observed due to the unique structure of the lipid portion A, present in the LPS molecule (Zhang *et al*., 2016; Raffray *et al*., 2019).

Despite the classification according to the antigenic characteristics of LPS, leptospires are also classified in several species defined by their degree of genetic relationship and determined by their genomic composition (Ko *et al*., 2009). Currently, according to the International Committee on Bacterial Taxonomy (LPSN - List of Prokaryotic names with Standing in Nomenclature), the genus *Leptospira* comprises 28 different genomic species. Twelve species belong to the pathogenic group (*L. interrogans, L. kirschneri, L. noguchii, L. borgpetersenii, L. alexanderi, L. weilii, L. santarosai, L. kmetyi, L. alstoni, L. mayottensis, L. stimsonii*, and *L. yasudae*), seven to the intermediate group (*L. licerasiae, L. wolffii, L. fainei, L. broomii, L. inadai, L. venezuelensis,* and *L. johnsonii*), and nine to the apathogenic group (*L. idonii, L. meyeri, L. terpstrae, L. biflexa, L. vanthielii, L. yanagawae, L. wolbachii, L. ellinghausenii*, and *L. ryugenii*) (Parte, 2018).

With the progress of genomic studies, the description of new species and serovars is increasing and consequently the taxonomy of the genus *Leptospira* is constantly changing (Thibeaux *et al*., 2018; Vincent *et al*., 2019).

Transmission

The transmission of leptospirosis occurs mainly through direct or indirect exposure to the urine of infected animals. The main entry points for leptospirosis in humans include cuts, abrasions, and conjunctival, oral, or genital mucosas. Intake of contaminated food also represents an important pathway for transmission of the pathogen (Ikbal *et al*., 2019; Karpagam & Ganesh, 2020). The bacteria released through rodent urine is present in ponds, rivers, puddles, sewers, agricultural fields, wet soils, among others. The number of cases of leptospirosis related directly to the amount of rainfall, which makes this a seasonal pathology in temperate climates whereas a permanent disease present all year round in tropical climates (Cunha *et al*., 2019).

In the rural perimeter, agriculture and livestock are the main risk factors for contracting leptospirosis due to precarious housing and inefficiency or lack of basic sanitation, determinant factors of an increased risk of infection. The risk of contracting leptospirosis also depends on the disease transmission and frequency of exposure in these communities (Karpagam & Ganesh, 2020; Soo *et al*., 2020). In addition to contact with animal urine, studies have also shown that leptospirosis can also be transmitted through the semen from infected animals (Adler, 2015; Ellis, 2015).

The main hosts of leptospires are mammals, however, reptiles and cold-blooded animals such as frogs, snakes, and turtles have demonstrated their ability to host pathogenic serovars (Lindtner-Knific *et al*., 2013). Among the host animals, the species *Rattus norvegicus*, popularly known as rat, and *Rattus rattus*, known as black rat, are the main hosts responsible for human infection in Brazil. In these animals, leptospires colonize the proximal renal tubules, being excreted into the environment through urine, without causing the death of this host (Ikbal *et al*., 2019).

The contamination in humans occurs mainly through contact with water or soil contaminated with the urine of infected animals. Exposure of individuals at risk of direct contact with potentially infected animals is also high. Professionals such as veterinary doctors, slaughterhouse workers, farm workers (mainly milking animals), animal shelter workers, scientists and technologists that handle animals in laboratories are more vulnerable to the pathogen. The magnitude of the risk depends on the exposure, so the correct use of personal protective equipment (PPE) in these higher risk professions is important (Adler, 2015).

In Brazil, the slums are one of the main risk areas for leptospirosis transmission because they present precarious conditions in terms of basic sanitation infrastructure, with no conditions for waste collection, as well as sewage treatment, and water supply. In addition, areas prone to flooding concentrate the majority of low-income populations, which makes them more vulnerable to climate variability and, consequently, with the highest concentration of cases and transmission of leptospirosis (Guimarães *et al*., 2014; Chaiblich *et al*., 2017).

Another important epidemiological data is on human-to-human transmission, which is extremely rare. Exceptionally, leptospirosis can be transmitted through organ transplantation or placental infection (Puliyath & Singh, 2012; Song *et al*., 2016).

Pathogenesis

Although the first report of leptospirosis occurred approximately two centuries ago, its pathogenesis is still not completely elucidated. However, several studies have advanced in understanding its mechanisms of action in the human body (Karpagam & Ganesh, 2020).

In infected animals, leptospires remain preferentially in the kidneys, presenting various symptoms, which may evolve into chronic renal failure (Ellis, 2015). In humans, leptospires are capable of rapidly invading the human body by entering the bloodstream, causing sepsis, resulting in severe inflammatory symptoms such as high fever, myalgia and superficial lymphadenectasis (Haake & Levett, 2015; Chou *et al*., 2018).

In many cases, pathogens travel from the bloodstream to the lungs, kidneys, liver, and cerebrospinal fluid, causing diffuse pulmonary hemorrhage, meningoencephalitis, and severe renal and hepatic failure. Leptospirosis in humans is known as the disease of Weil, and the development of jaundice resulting from the high levels of bilirubin in the blood is common. This, associated with hemorrhagic conditions, is regarded as the most important clinical feature of this disease (Adler, 2015; Haake & Levett, 2015; Kaya *et al*., 2020).

Recent studies have pointed out leptospirosis as a systemic inflammatory response syndrome (SIRS) due to the high amount of inflammatory cytokines present in its carriers, although the pathophysiology of pathogenic leptospirosis still remains little known (Yilmaz *et al*., 2015; Chirathaworn *et al*., 2016; Picardeau, 2017).

Medicinal plants

The use of medicinal plants in cultures and traditional medicine has occurred since prehistoric times. Plants with therapeutic potential are present in all cultures and their use may be either a supplement or the basis for drug development. In recent years, their use has become increasingly common due to their bioavailability, with natural products and derivatives already accounting for more than 50% of all medicines for clinical use in the world (van Wyk & Wink, 2018).

A plant is medicinal when the purpose of its use targets the maintenance of health, both in traditional and modern medicine. These plants may be used as a whole or in parts when their pharmacological therapeutic potential is verified. However, as a single species may contain a variety of phytochemical properties, the effects of using an entire plant as a medicine are uncertain (Ahn, 2017).

In many countries and regions, the use of medicinal plants is generally one of the only available resources, both because of the high costs in producing medicines and due to the vulnerability of populations in developing countries. Consequently, the use of most plant species occurs only because of historical and cultural knowledge passed down through generations, without scientific evidence on the efficacy and safety of their use (Petrovska, 2012; Jamshidi-Kia *et al*., 2018; van Wyk & Wink, 2018).

The economic vulnerability associated with difficulties in the access to health care by the poorest population contributes to the use of medicinal plants. In Brazil, the investment in policies and studies that seek phytotherapeutic alternatives increase every year, since it is a developing country with a vast botanical diversity. This direction was one of the bases for the creation of the List of Medicinal Plants of Interest of the Brazilian Unified Health System, the Renisus list (Mendonça, 2014; Bittencourt *et al*., 2020).

In many countries, there is little regulation of traditional medicine, but the World Health Organization has made efforts to develop a coordinated support network in order to encourage the safe and rational use of these bioavailable natural resources. Medicinal plants face general threats, such as climate change and habitat destruction, so the WHO also presents certain types of care for the cultivation of these medicinal plants, in order to validate and guarantee their use as a complementary therapeutic source in medicine (WHO, 1999; WHO, 2004; WHO, 2019).

In Brazil, in 2009, following the recommendations of the WHO, the Renisus list was created, with the objective of listing as plants with medicinal potential according to previous empirical and scientific knowledge, providing resources for studies that validate the efficacy and guarantee the safety of use. In addition, it can contribute to the inclusion of these plants in a complementary way as therapies present in the public health network. Currently, about 71 users are present in this list (de Almeida *et al*., 2020).

Most medicinal plants have many different compounds, some of which are of great complexity. Phytochemical components include flavonoids, alkaloids, anthraquinones, glycosides, phenols, saponins, steroids, tannins, terpenoids, and many other metabolites that are responsible for their medicinal properties and are present in the flowers, leaves, bark, fruits, seeds, and along their whole structure (Pattayak *et al*., 2017).

In order to ensure the quality of natural herbal medicines some pre-established criteria in pharmacopoeias are followed for all plants, whether or not included in the Renisus list. Among these criteria are the correct identification of plant species, the analysis of purity of compounds, active principles and adjuvants, as well as safe levels of concentration of the botanical material (Palhares *et al*., 2015).

Toxicity and safety of medicinal plants

One of the main criticisms regarding the production of herbal medicines and herbal food supplements relates directly to the lack of sufficient scientific evidence to ensure safety, efficacy, and low toxicity. Recent studies have shown that one third of the herbal products tested did not contain information on the herbs and their active ingredients listed on the labels, but also some of them were adulterated products or products with unlisted components, including the presence of possible allergens (Coghlan *et al*., 2012; Zhang *et al*., 2012; Newmaster *et al*., 2013).

The use of medicinal plants or drugs and herbal therapies may cause side effects due to their active substances, adulteration, contamination, overdose, or by incorrect prescription. Many of these effects are known, although several others still require scientific studies for evidence. Since it is a product of natural origin, a false sense of safety may arise, being also a risk for the occurrence of side effects. However, the existence of natural poisons such as nicotine is an evidence of the opposite (Brima, 2017; Shankar, 2017; Subramanian *et al*., 2018).

Problems with incorrect identification, variations in composition, contamination with microorganisms or intoxication by pesticides and heavy metals are also safety and quality issues related to the traditional use of natural plants, especially when they are consumed in their whole form. This consumption without previous knowledge may result in situations of adverse reactions and may cause other health problems (Heinrich *et al*., 2017).

Medicinal plants used in leptospirosis studies

Alternative therapies for the treatment of leptospirosis, such as the use of validated medicinal plants, are still limited. However, in the last decade, some scientific studies have aimed to study the mechanisms of action of plants and their bioactive compounds in the treatment of leptospira pathogens, both to elucidate the mechanisms of action (Chandan *et al*., 2012; Divya *et al*., 2013; Seesom *et al*., 2013; Mustafa *et al*., 2018).

During 2012 to 2020, the search recorded nine English articles on the use of medicinal plants against leptospirosis, one in the Capes database, two in Pubmed, and six articles in Google Academic. In Portuguese and Spanish idiom, none of the pre-established search terms returned results. Among the localized studies, seven were developed exclusively in India, showing that this country is widely recognized for its rich culture in the use of medicinal plants, in which the majority of its population relies on herbaceous plants to supply its therapeutic needs (Tyagi *et al*., 2016).

Considering the prevalence of leptospirosis in underdeveloped regions, this article reveals and remarks the importance of developing research to expand the use of medicinal plants as a natural therapy against leptospirosis, in order to assess its safety and efficacy of use. Researchers must also overcome a recurring complaint, related to the lack of quality of studies based on the development of natural medicines, in addition to considering economic factors for the development and implementation of therapies based on bioavailable resources (Pelkonen *et al*., 2014).

It is important to highlight that all the studies found in the databases checked for antimicrobial activity against *Leptospira* spp. Some of them used the extracts of *Boesenbergia rotunda* (Chinese Ginger) and *Andrographis paniculata* (Sherita green), presenting a stronger effect than standard antibiotics, being more effective and less toxic, such as Doxycycline (Punnam Chander *et al*., 2016; Arulmozhi & Kalimuthusamy, 2017).

Other plants have also proven their antibacterial potential against different pathogenic serovars in vitro test, including *Phyllanthus amarus* (Stonebreaker), *Eclipta alba* (Watercress), *Garcinia mangostana* (Queen of fruits), *Adhatoda vasica* (Malabar nut), *Glyptopetalum calocarpum* (Miroonlő), and *Quercus infectoria* (Oak twig). Although the extract compositions present variations, all these plants in their respective studies showed positive results in treatment of pathogenic serovars of *Leptospira* spp. (Saravan *et al*., 2012; Chandan *et al*., 2012; Seesom *et al*., 2013; Nelson *et al*., 2013; Divya *et al*., 2013; Chander *et al*., 2015; Mustafa *et al*., 2018).

It is important to highlight that the characteristics of the plant material always must meet the criteria of selectivity, solubility, cost, and safety. The particle size and division, and the solvent used, are crucial for the development of effective and selective methods for the extraction and isolation of the active principles found in medicinal plants (Zhang *et al*., 2018).

Regarding the composition of the extracts from the studies presented in this article, the two main extraction methods used to obtain the active principles of the plants were the aqueous extract and the alcoholic extract, representing 77% of the methods, with the leaves being the most used part, with 55% of them. Although this is an expressive number, it is important to highlight that, for each type of plant or part of it, the extraction method may change, always according to the safety and efficacy standards (Oreopoulou *et al*., 2019). Table No. 1 presents all studies included in this review in accordance with the established methodology.

Table No. 1
Plants used against *Leptospira* spp. infection

Popular Name	Part Used	Objective of the Study	Extract composition	Results of the study	Place	Reference
Phyllanthus amarus (Stonebreaker)	Whole plant	Evaluate the effect of *Phyllanthus amarus* extract on the SphH gene of Autumnalis serovar	Aqueous extract	*Phyllanthus amarus* extract has been effective in damaging leptospires DNA, preventing the amplification of the most virulent gene (SphH)	Tamil Nadu, India	(Saravanan *et al*., 2012)
Eclipta alba (Watercress) *Phyllanthus amarus* (Stonebreaker)	Whole plant	Evaluate the anti-leptospiral and antioxidant action of *Eclipta alba* and *Phyllanthus amarus*	Aqueous and methanolic extract	Both extracts presented an inhibitory action against various *Leptospira* serogroups, and also antioxidant potential	Karnataka, India	(Chandan *et al*., 2012)
Garcinia mangostana	Fruit	To evaluate the anti-leptospiral activity of	Raw ethyl acetate and	The combination of γ-mangostine and	Chantaburi Thailand	(Seesom *et al*., 2013)

(Queen of fruits)		*Garcinia mangostan*a associated with penicillin G	ethanolic extract	penicillin G generated synergistic effect that improved the efficacy in the treatment of leptospirosis		
Adhatoda vasica (Malabar nut)	Leaves	To evaluate the inhibitory action of *Adhatoda vasica* extract in the formation of *Leptospira interrogans* inclusion bodies	Alcoholic extract	The adhatode extract decreased the inclusion body reduction in the leptospira cells contributing to the loss of virulence of the serovar	Western Ghats, Tamil Nadu India.	(Nelson *et al.*, 2013)
Eclipta alba (Watercress)	Leaves	Evaluate the action of *Eclipta alba* extract on Autumnalis serovar proteins	Aqueous extract	Aqueous extracts of *Eclipta alba* were effective in causing damage to the leptospires proteins	Tamil Nadu, India	(Divya *et al.*, 2013)
Glyptopetalum calocarpum (Miroonlő)	Leaves	Evaluate anti-leptospiral activity of *Glyptopetalum calocarpum*	Alcoholic extract	Of the six compounds tested, lupenone and stigmasterol, showed anti-leptospiral activity in vitro	Adaman and Nicobar, India	(Chander *et al.*, 2015)
Boesenbergia rotunda (Chine se ginger)	Leaves	Evaluate anti-leptospiral activity in *Boesenbergia rotunda*	Methanolic extract by percolation	The anti-leptospiral activity of *B. rotundra* in minimum inhibitory concentration is higher than that of standard antibiotics	Adaman and Nicobar, India	(Chander *et al.*, 2016)
Andrographis paniculata Nees (Sherita green)	Leaves	Evaluate the anti-leptospiral action of *Andrographis paniculata Nees* extract in 5 serovars	Ethanolic sxtract	The ethanolic extract was more effective and less toxic than Doxycycline in the serovars tested, *L. interrogans* australis and *L. interrogans* icterohaemorrhagiae,	Tamil Nadu, India	(Arulmozhi & Kalimuthusamy, 2017)
Quercus infectoria (Oak twig)	Branches	To evaluate the antimicrobial activity of *Quercus infectoria* extract against pathogenic leptospires	Aqueous extract	The aqueous extract of *Q. infecoria* presents antimicrobial activity against the sorovars of *L. interrogans*	Kota Bharu, Malaysia	(Mustafa *et al.*, 2018)

Source: Elaborated by the authors

FINAL REMARKS

The use of medicinal plants is an important alternative to the current treatment of leptospirosis. The discovery of plant compounds with active principles capable of combating the various *Leptospira* spp serovars is of extreme importance considering the high prevalence of this pathology in populations from developing regions and countries with no basic sanitation conditions.

Although there are some listed plants in the literature with antimicrobial potential against leptospires, studies are still scarce. India stands out with the largest number of studies and listed plants with potential therapeutic properties and this data demonstrates the national interest in using its natural resources in the treatment of leptospirosis. It is also important to note that all the studies published between 2012 and 2020 had promising results, since all the plants described presented anti-leptospire potential.

However, to ensure low levels of toxicity, safety, and especially efficacy in the treatment of leptospirosis, further scientific studies are needed to analyze the mechanisms of action of plants with medicinal potential, and thus validate their use against the pathogenic serovars of *Leptospira* spp.

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