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Review Article

# *PHYLLANTHUS NIRURI* L. (STONE-BREAKER) AS AN ALTERNATIVE OF ANTI-HUMAN DISEASES, ANTIMICROBIAL AGENT, AND ITS APPLICABILITY TO COMBAT RESISTANT MICRORGANISMS. A BRIEF REVIEW.

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**Informações do artigo**

Palavras-Chave:
*Phyllanthus niruri* L.;
Microbioma; *Candida* spp.

**Resumo**

O microbioma humano sofre variação nas mais diversas regiões do nosso corpo, de acordo com as condições a qual está exposto, sendo de vital importância para a saúde humana. Apresenta diversas condições que podem promover o estabelecimento de microrganismos e em desequilíbrio favorecem o desenvolvimento de microrganismos patógeno-oportunistas, o conhecimento da distribuição destes microrganismos nos diferentes órgãos e seu papel biológico conduz a um melhor entendimento da sua complexa dinâmica, aprimorando o desenvolvimento de novas formas de diagnóstico e até mesmo de tratamento de certas patologias. Dentre as patologias mais estudadas na atualidade podemos citar as infecções ocasionadas por fungos são uma das áreas amplamente estudadas. Estes microrganismos estão se tornando cada vez mais resistentes aos tratamentos convencionais, aumentando os relatos de resistência, especialmente as espécies de *Candida,* que apesar de estar presente na flora normal do organismo humano vêm causando diversos casos de contaminação e infecções, denominados candidoses na literatura. Devido ao aumento da resistência aos tratamentos antifúngicos convencionais é necessário a elaboração de estratégias que possam prevenir e tratar a disseminação destes microrganismos. Para isso, estudos alternativos com plantas medicinais vêm crescendo e ampliando o entendimento e aplicabilidade de novos compostos com finalidades

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antimicrobianas, visto que, há milênios a humanidade utiliza plantas para tratamento de diversos tipos de doenças e esse conhecimento tradicional facilita a busca de alvos de pesquisa de componentes naturais provenientes de plantas, permitindo a comprovação científica desses efeitos terapêuticos. Este trabalho tem por objetivo um levantamento bibliográfico das aplicabilidades da planta de *Phyllanthus niruri* L. (Quebra-pedra), frente aos desafios da ciência ao desenvolver novas fontes de combate a microrganismos resistentes.

## Article ID

Key words:
*Phyllanthus niruri* L.;
Microbioma; *Candida* spp.

## Abstract

The human microbiome undergoes variation in the most diverse regions of our body, according to the conditions to which it is exposed, being of vital importance for human health. It presents several conditions that can promote the establishment of microorganisms and in imbalance favor the development of opportunistic pathogens, the knowledge of the distribution of these microorganisms in different organs and their biological role leads to a better understanding of their complex dynamics, improving the development of a new one forms of diagnosis and even treatment of certain pathologies. Among the most pathologies studied today, we can mention infections caused by fungi is one of the widely studied area. These microorganisms are becoming increasingly resistant to conventional treatments, increasing reports of resistance, especially the *Candida* species, which despite being present in the normal flora of the human organism have been causing several cases of contamination and infections, called candidosis. Due to the increased resistance to conventional antifungal treatments, it is necessary to develop strategies that can prevent and treat the spread of these microorganisms. For this, alternative studies with medicinal plants have been growing and expanding the understanding and applicability of new compounds with antimicrobial properties, since, for millennia, makind has used plants to treat various types of diseases and this traditional knowledge facilitates the search for research targets of natural components from plants, allowing scientific proof of these therapeutic effects. This work aims at a bibliographical survey of the applicabilities of the *Phyllanthus niruri* L. (stone-breaker) plant, in the face of the challenges of science when developing new sources to combat resistant microorganisms.

## Literature review

### Microbiome

Since birth, the human body is exposed to several microorganisms species, which are housed in various organs and tissues, such as skin, genitourinary and gastrointestinal systems, this interaction is called "microbiome" (Cardoso, 2015; Sender et al. 2016; Germano et al., 2018). The human microbiome consists of a complex diversity of microorganisms that colonize each individual, which may be commensal or pathogenic microorganisms, establishing a symbiotic relationship between the human organism and microorganisms, such as *Candida albicans* (Weber and Polanco, 2012; Cardoso, 2015; Wilson, 2018). A healthy human presents favorable and unfavorable conditions for the establishment of different species

and can contain approximately $3.8 \times 10^{13}$ microbial cells (Sender et al. 2016). Most of them are harmless throughout life for healthy hosts, remaining viable and active in the organs and can help in essential functions, such as digestion, induction of production of components used for metabolism and defense of the host, can also be used activity against pathogenic microorganisms. These characteristics demonstrate an important biological interaction with our microbiota (Cho and Blaser, 2012; Weber and Polanco, 2012; Cardoso, 2015; Sender et al., 2016; Gajdács et al., 2019).

Health and disease are closely linked to the normal human microbiota, the microorganisms inhabit the host without causing apparent damage or disease, however, under certain conditions of imbalance of the host, can cause some disturbances to the human body by differentiation and proliferation. When the host defence mechanisms are unable to eliminate them, they can spread through out the tissues and cause infectious diseases, which can eventually be serious (Lamont and Jenkinson, 2010; Cardoso, 2015; Germano et al., 2018).

**Oral Microbiome**

Soon after the birth of an individual, the oral microbiota begins to establish itself, where the microbial diversity and quantity will change in the course of their life (Santos Júnior and Izabel, 2019). Because this location is the beginning of the digestive system, it is considered as the gateway to the human organism, where some microorganisms can enter and establish. In this environment, microorganisms are mixed with saliva, proteins and enzymes in the digestion process, which can hinder their eradication and study in different environments due to the presence of different components present in oral conditions (Silva, 2016; Campo, 2018).

The oral cavity of an individual is cohabited by several microorganism's species that live in the various regions of the interior of the mouth (tongue, teeth and others) (Cardoso, 2015). Each individual can have different types of microorganisms, which in balance maintain the oral and general health of the host organism. However, when the host organism is affected, its health is impaired and these microorganisms take advantage, becoming pathogenic; this is what happens in fungal infections, usually caused by *Candida* species, which can favor or promote some diseases such as dental caries and periodontal diseases (Cardoso, 2015; Silva, 2016; Campo, 2018; Wilson, 2018; Gajdács et al., 2019). The imbalance between the host and the microbiota can promote infections and other types of diseases such as pericarditis, pneumonia, gastric ulcer, coronaritis, and many more (Cardoso, 2015; Silva, 2016; Campo, 2018; Gajdács et al., 2019). The presence of unbalanced *Candida* spp in the host can promote the formation of dental biofilm, which can be co cultured with bacteria, can be colonize in different places of the oral cavity, such as tongue, gums, labial mucosa and palate, and can adhere to oral prostheses or implants, forming a layer composed of numerous microorganisms (Peixoto et al., 2010; Campo, 2018).

***Candida* spp.**

Taxonomically, approximately 200 species of *Candida* are described in the Fungi Kingdom, division Eumycota, subdivision Deuteromycotina, however some species are grouped in the subdivision Ascomycotina, class Blastomycetes and Family Cryptococcaceae (Santana et al., 2013).

The cell structure of fungi is similar to that of other eukaryotic organisms, consisting of a cell wall composed mainly of polysaccharide chitin, being a relatively rigid and dynamic structure, which provides several essential properties to the cell by maintaining the cells shape and providing the osmotic support. Other important functions of cell wall are physical protection, is related to cell signaling, adhesion to surfaces and reproduction etc. This structure is also composed of a phospholipid membrane, with predominating ergosterol, cytoplasm with organelles, vacuoles and the nucleus with stored genetic material (Fukuda et al., 2009; Santana et al., 2013). Microorganisms of the genus *Candida* are yeast-like, unicellular eukaryotic fungi. Their morphology can be oval, rounded or elongated with asexual reproduction by budding, called blastoconidia (Santana et al., 2013).

For most *Candida* species, two distinct morphological forms can be identified, namely blastopores and hyphae, these two morphological forms has a high potential to produce solid and resistant biofilms, causing serious infections (Álvares et al., 2007; Purisco, 2010; Simões et al., 2013; Ruiz and Pereira, 2016, Quindós et al., 2018). This fungi

have an accelerated development, quickly forming extensive biofilms on different surfaces of the host, including the oral mucosa that, together with the constant salivary production and the consumption of foods that serve as a source of nutrients for microbial growth, This microorganism has the ability to adhere and form germ tubes, which can cause disease in the host by tissue invasion, production of extracellular proteases, induction of hypersensitivity or production of toxins and the formation of biofilm. (Lamont and Jenkinson, 2010; Silva, G., 2013; Bath et al., 2014; Silva, 2016; Oliveira, 2019).

Infections caused by the genus *Candida*, are referred as candidiasis or, more recently, candidosis in the literature. They are caused by fungi that proliferate rapidly, form extensive biofilms on different surfaces of the host, including the oral mucosa with the favor of constant salivary production and the availability of high concentrations of nutrients for microbial growth. The biofilm structure, formed by these fungi, can also be installed in hospital and personal devices, such as catheters and prosthetic surfaces or devices (Lamont and Jenkinson, 2010; Bath et al., 2014). In elderly and immunosuppressed patients, the conversion of normal oral *Candida* into an infectious pathogen can be much more harmful, forming biofilms on mucous membranes and on prosthetic surfaces, where infected oral prostheses cause prosthetic stomatitis in most cases associated with erythematous candidiasis (Silva, 2013; Bath et al., 2014).

Candidiasis can be mucous, cutaneous-mucous, cutaneous or visceral, with optimal growth in moist and warm areas, which affect vaginitis, dermatitis and candidiasis. These manifestations of the disease do not normally cause a threat to the life of the host, but they represent a socioeconomic problem of high importance. Cutaneous candidiasis and chronic mucosal infections are associated with low activity of the immune system, individuals with hereditary immunological defects and carriers of the human immunodeficiency virus or iatrogenic. Chronic vaginal candidiasis is affected by several factors, such as diabetes mellitus, pregnancy, antibiotic therapy, among others. And disseminated candidiasis is associated with a low neutropaenia, leukemia, chemotherapy or immunosuppression in post-transplant patients (Álvares et al., 2007).

Currently, infections caused by *Candida* spp. can vary from superficial lesions to serious and widespread infections, having great importance for the frequent incidence with which they colonize and infect the human body, corresponding to approximately 80% of the infections caused by fungi registered in hospitals, where half of these infections turn into candidemia (blood infection caused by the fungus *Candida* spp.), representing a high mortality rate (Colombo and Guimarães, 2003, Álvares et al., 2007; Sá Silva et al., 2009; Ruiz and Pereira, 2016).

About 10% of these microorganisms are considered to be etiological agents in human infections, generally characterized as opportunistic microorganisms present on the mucous surface and skin of human beings (Santana et al., 2013), where they are commonly found in the gastrointestinal system of 80% of the healthy population, and 30% of the female population has colonization by *Candida* spp. in the vaginal mucosa (Colombo and Guimarães, 2003).

Clinically they are not pathogenic to humans, but are classified as opportunistic pathogens, as they have the potential to invade hosts, becoming responsible for many cases of hospital infections and high mortality, especially in patients with low immune system activity. The *Candida* contamination corresponds to 80% of fungal infections registered in hospitals, and eradication in health sectors is essential due to the manifestation of the infection and the rapidly colonization (Colombo and Guimarães, 2003; Cardoso, 2015; Silva et al., 2014; Ruiz and Pereira, 2016).

Infections of the genus *Candida* represent a growing problem in the areas of public health, increasing the length of patients hospitalization and increasing the hospital cost (Menezes et al., 2012; Costa and Santiago, 2016). Thus, due to the increased incidence over the years the rate of morbidity and mortality caused by *Candida* spp. has become a fact. The pathogenic power of *Candida* spp. has been particularly well studied in *C. albicans* (Cardoso, 2015; Silva et al., 2014; Ruiz and Pereira, 2016).

The study of the *Candida albicans* is extremely important due to its virulence factors. And medicinal plants are very important for the development of natural drugs for treatment. Although there are drugs used against the *Candida* spp, making them less susceptible to these drugs, which produce low susceptibility to the treatment, due to the development fungal resistance (Barbedo and Sgarbi, 2010; Costa and Santiago, 2016; Liu et al., 2016; Silva, 2017; Revie et

al., 2018). Incorrect use of available antimicrobials can also increase the toxicity to the host, action spectrum problems and side effects. Assessing and monitoring the susceptibility of these microorganisms is of great importance in order to reduce the risk of spread and avoid resistance. On the other hand, the importance of related research in the discovery of novel compounds that act against these microorganisms is development of new strategies to prevent, reduce or assist treatment against fungal infections (Bergold and Georgiadis, 2004; Costa and Santiago, 2016; Liu et al., 2016; Silva, 2017; Revie et al., 2018).

**The use of natural products as an alternative therapeutic agent**

Medicinal plants are considered to have therapeutic action, based on popular or scientific knowledge. Herbal medicines are prepared only by plant species, with no mixing with synthetic compounds (Oliveira, 2016).

The use of plants for medicinal purposes was one of the first treatment resources used against diseases by ancient people, which have been scientifically improved since then (Braz et al., 2015; Buso Ramos, 2016). Since ancient times, empirical knowledge about the use of plants has been observed and passed from generation to generation by different ethnic groups, used for treatments and disease prevention (Escola de Saúde Pública, 2018; Silva, 2008).

In several countries, mainly in the populations which has little or no access to conventional medicines, treatment based on empirical knowledge has been adopted as a form of prevention and cure for many diseases (Leão et al., 2017). In Brazil, knowledge about the use of medicinal plants was acquired through indigenous practices, as well as practices derived from the knowledge of immigrants and also by slaves, which has become a traditional folk medicine, which has recently been recognized by the World Organization of Health (Escola de Saúde Pública, 2018). Brazil has the highest plant biodiversity in the world, with more than 60,000 species cataloged, of which only 8% have been researched on biotic and medicinal compounds (Salomé, 2007).

In 1991, the WHO (World Health Organization) reported the necessary contribution of traditional folk medicine in social assistance, mainly to inhabitants with little accessibility to health systems and began to encourage the use of proven and studied medicinal plants, showing that 80 % of the population uses plants to relieve unpleasant symptoms or pain (Salomé, 2007). The approval of the National Policy on Integrative and Complementary Practices (PNPIC) and the National Policy on Medicinal and Herbal Plants (PNPMF) allowed the implementation of phytotherapy in the Unified Health System (SUS), allowing users of health services to know and use the medicinal herbs, ensuring that the values and traditions passed on between generations are preserved and that the use of plants occurs correctly and safely, balancing the existing strands between traditions and innovations. Medicines derived from plant materials have a great importance in global health. Also, this knowledge has been maintained for generations because of the continuous and natural supply of phytomedicines, being an effective alternative to the antimicrobial resistance which is currently frequent in Brazil. Indiscriminate and excessive use of antimicrobials are key reasons for the development of this resistance. Further phytomedicinal products have low side effects and they are cost effective (Brasil, 2006; Martins et al., 2012; Queiroga, 2015; Brasil, 2016).

The use of medicinal plants in health systems has become increasingly relevant to public health, allowing social inclusion and impacting the country's productivity, also allowing to preserve the culture of a people and care for the environment. Medicinal plants can be used as a strategy for innovation, knowledge, used as a way of preventing diseases and contributing to the advancement of scientific research (Feiria, 2015; Queiroga, 2015; Boni, 2016; Buso-Ramos, 2017; Anibal et al., 2017; Barbosa, 2018; Oliveira, 2019).

Medicinal plants are proven to be the source of several natural antioxidants, an extensive variety of secondary metabolites (Martins et al., 2012). Its compounds also have several types of biological activities, including antifungal, antimicrobial, antitumor, antiparasitic, anti-inflammatory, healing, and many others (Nunes et al., 2016). They are considered one of the main sources for the development of therapeutic agents for several conditions, including for infectious diseases (Silva, 2008; Buso-Ramos,2017).

Recently, plants are being studied more and more in order to demonstrate their therapeutic potential and to find less aggressive and efficient treatments that help in conjunction with drugs or decrease

the resistance acquired by microorganisms to antimicrobials already used, thus research with plants has been showing of great importance to combating infections (Martins et al., 2012; Nunes et al., 2016).

In this context, the *Phyllanthus* genus is investigated, especially in this work the species *Phyllanthus niruri*, that has shown wide biological activity and great therapeutic potential, justifying the exploration of this plant in research.

***Phyllanthus* spp.**

The classification of the genus consists of: Kingdom: Plantae; Division: *Angiosperm*; Class*: Dicotyledonous*; Order: *Tubiflorae*; Family: *Euphorbiaceae / Phyllanthaceae*; Subfamily: *Phyllanthoideae,* Tribe: *Phyllantheae,* Subtribe: *Flueggeinae,* Genus: *Phyllanthus* (Rehder et al., 2003; Silva and Sales, 2004).

The genera was first referred by Linnaeus, in 1737 in the book "Systema Naturae", but it was only established later by the same author in 1753, in the book "Species Plantarum" (Silva and Sales, 2004). The genus *Phyllanthus* (from the Greek phyllon: leaf and anthos: flower) is made up of herbs, shrubs or monoecious or dioecious trees, comprising more than 8,000 species spread over most continents (Sarin et al., 2014), being considered the most diverse and the largest genus of the Euphorbiaceae family because the diversity of vegetative and floral characteristics (Kassuya et al., 2003; Rehder et al., 2003; Torres et al., 2003, Martins et al., 2014; Falcon et al., 2019).

The *Phyllanthus* genus is prevalent in tropical and subtropical regions, in the most diverse types of vegetation (Rehder et al., 2003). It can be found in the American, African, Asian and Australian continents. In South America, Brazil is the country wich contains the largest number of species, approximately 100 species, where 40% of them are found in the southeastern states of Brazil, which comprises the country's *Phyllanthus* diversity center (Martins, 2013; Martins et al., 2014; Leão et al., 2017).

In Brazil they are called "Erva-pombinha" or better known as "Quebra-pedra" among other variations of popular name; the most common species are herbs: *Phyllanthus amarus* Schum. and Thonn, *Phyllanthus niruri* L. and *Phyllanthus tenellus* Roxb. Müll. Arg. Some species have a landscape character despite not being cultivated. However, in most cases, they are considered as weeds, invaders in agriculture and rural areas (Torres et al., 2003; Silva and Sales, 2004) where several species of the same genus grow together, causing confusion in their identification (Sarin et al., 2014). For this reason, they are called "species complexes", where a group of organisms share very similar phenotypic and morphological properties. Therefore, the classification based only on morphological characters may be erroneous. Within the *Phyllanthus* genus there is the "*P. niruri* complex", which comprises several taxa with leaf and floral characteristics extremely similar to the species *P. niruri* L. (Alonso and Amaral, 2010).

Previously, the species *P. amarus*, *P. fraternus* and *P. debilis* were grouped into a single group of the species *P. niruri*, mentioned as species of the "*niruri* complex". The genus *Phyllanthus* is paraphyletic, so there are two problematic and confused species: *P. niruri* and *P. amarus*, which are often confused, but are two individual species (Lee et al., 2006). Currently, it has been clarified that *P. niruri* is an American species. Thus, the identification of the species can often be mistaken, requiring the use of chemical and molecular markers to identify *Phyllanthus* species (Sarin et al., 2014). Although there are other species of the genus, called "Quebra-pedra", only *P. niruri* has officially proven medicinal properties (Farmacopéia Brasileira, 2010; Oliveira, 2016).

It has been used in the form of leaves infusion, stems and roots for the treatment of numerous disorders, as it has different diuretic, analgesic, anti-inflammatory, antimicrobial and antitumor properties (Torres et al., 2003). Plants of the genus *Phyllanthus* are commonly used to treat liver, kidney and bladder calculi. Also used to treat colds, asthma, bronchial infections, jaundice, dysentery, inflammation and genitourinary infections, such as herpes and gonorrhea, in addition to diabetes. Recently, it was discovered the possible application in the treatment against the acquired immunodeficiency virus (HIV), Hepatitis B and cancers (Kassuya et al., 2003; Rehder et al., 2003; Salomé, 2007; Messias et al., 2015). Extracts made with *Phyllanthus* species have been reported to have good pharmacological effects, such as anti-hepatotoxic, anti-hyperglycemic and anti-hepatitis B virus (Salomé, 2007; Sarin et al., 2014).

Thus, the purified active compounds obtained from different *Phyllanthus* species have demonstrated antinociceptive activity, against hepatitis, inflammation and allergies (Kassuya et al., 2003; Torres

et al., 2003; Salomé, 2007). Most plants belonging to the *Phyllanthus* genus have several combinations of secondary metabolites and more than 50 compounds that classify them as medicinal plants (Sarin et al., 2014; Oliveira, 2016), as the beta-sistoterol compound among others, which acts on calculi prevention, inhibition and elimination, in addition to anti-inflammatory and analgesic activity (Kassuya et al., 2003; Sarin et al., 2014; Oliveira, 2016). The high quantity and efficiency of the components present in the plant make it a medicinal plant that is commonly used for preventive and curative treatments (Braz et al., 2015).

The study of phytochemical components have a great importance, since it recognizes the phytochemical compounds abundant in the plant species of interest, identifying the most present, relevant and useful compounds and secondary metabolites found in medicinal plants (Bessa et al., 2013). The use of ethnobotanical information and pharmacology helps in the search for bioactive compounds existing in medicinal plants, considering agrotechnological, biotechnological, pharmacological and microbiological parameters (Bessa et al., 2013). Within the *Phyllanthus* genus, there is a great variety of metabolites and the potential for the treatment of various pathologies. To prove the beneficial effects of the plant reported by popular medicine, several countries have been studying the plants of this genus (Salomé, 2007).

***Phyllanthus niruri L.***

The *Phyllanthus niruri* species has a variety of popular names, such as: "stone-breaker, pigeon-weed" and "burrow-wall" among others, but the best-known common name is "stone-breaker" in portuguese "Quebra-pedra". It is the species of the genus with greater use in traditional medicine (Braz et al., 2015), it is a weed with 30 to 60 cm in height, grows in any type of soil, as well as growing between stones, walls, and cracks and it can be found with flower and with fruits throughout the year in all Brazilian states. It is native to the Amazon and other tropical regions of Brazil and the world, such as Nigeria, Ghana, Bahamas, India, China, among others (Girach et al., 1994; Oliveira, 2016; Leão et al., 2017). It is considered as a "weed", because of its wide distribution, rapid proliferation and adaptability, which allows its incidence in several regions of the world (Silva and Sales, 2004).

According to the Brazilian Pharmacopoeia, the species is characterized as herbaceous, glabrous, with branched or simple stems, the main branches are thin with no leaves, with lateral branches with alternating, opposite, simple, membranaceous, glabrous, oblong-elliptical leaves, of attenuated apex, of olive-green color and pale green abaxial face. When looking at the leaves together they appear to be composed, with blades 0.95 cm long and up to 0.6 cm wide, and petioles with a maximum length of 0.1 cm. They have schizocarpous fruits, of the tricoca type, with 0.1 cm to 0.25 cm in diameter, globose, exposed to the abaxial region of the branches, separating into carpids; olive green, membranous and verrucous endocarp; 2 seeds per lotus, triangular, with the ventral faces straight and the dorsal face rounded, warty, prominent warts, with acute to rounded apex; cylindrical pedicels, approximately 0.5 cm long at maturity; persistent, membranous chalice, developed. The macroscopic characteristics of *Phyllanthus niruri* are decisive to distinguish them since the species can be very similar to others when observed with the anatomical characteristics (Farmacopéia Brasileira, 2010; Martins et al., 2014).

Currently, it is present in the National List of Medicinal Plants of Interest to SUS-RENISUS, with high productive potential for the Ministry of Health of Brazil, which suggests studies to subsidize the preparation of herbal products and advises on the use of medicinal plants made available for the population (Queiroga, 2015; Escola de Saúde Pública, 2018). Although other species of the genus are also called "Quebra-pedra", only *P. niruri* has officially proven medicinal properties (Farmacopéia Brasileira, 2010; Oliveira, 2016), which does not cause psychological, physical changes or blood toxicity, does not showing results related to the toxic effects of the product (Braz et al., 2015).

Initial studies with *P. niruri* were performed by Brazilians researchers, since this plant is native to the country. The plant has a long history of use by Brazilians against several kind of diseases (Kaur et al., 2017), featuring various chemical compounds that have biological activities, what makes this plant considered as a medicinal plant with high therapeutic potential for preventive and curative treatments (Lorenzi e Matos, 2002; Salomé, 2007; Marques, 2010; Cruces et al., 2013; Escola de Saúde Pública, 2018).

Among these activities, is the antimicrobial capacity is one of the major therapeutic use of *P. niruri* due to presence of antimicrobial components. Some authors have demonstrated the ethyl esters have an antimicrobial activity against oral microorganisms, *S. mutans, S. gordonii, P. gingivalis, F. nucleatum* e *C. albicans* (Huang et al., 2010). The ethyl ester of hexadecanoic acid and ethyl ester can be found in various plant extracts of the plant and act as hemolytic, pesticide, antioxidant, in addition to having antifungal and antibacterial action (Tyagi e Agarwal, 2017), especially on the yeast *C. albicans* (Santos Primo, 2013; Anibal et al., 2017).

The presence of metabolites and other compounds in the *P. niruri* plant, such as fatty acids, steroids, hexadecanoic acid ethyl ester (palmitic acid) and linolenic and linoleic acid ethyl ester, it assist in antioxidant and anti-inflammatory functions, as well as anti-acne, antihistamine, hemolytic, antiandrogenic, antiparasitic or nematicide, in addition to presenting antimicrobial activity (Santos, 2017; Tyagi e Agarwal, 2017).

The beta-sitosterol compound present in the *P. niruri* plant was antinociceptive and anesthetic potential, also has effective against several microbial species, such as *S. aureus, S. pyogenes, B. subtilis, P. aureginosa, S. typhi* e *C. albicans* (Acikara et al., 2014; Odiba et al., 2014; Sarin et al., 2014; Yinusa et al., 2016). Phytol also present in this plant has been shown anti-inflammatory, antinociceptive and antimicrobial (Leite, 2010; Ghaneian et al., 2015; Tyagi e Agarwal, 2017).

This species has been widely used in Brazilian popular medicine as a therapeutic treatment against various diseases, where research carried out in the last 35 years with cells and animal models has provided the knowledge of valuable scientific evidence that demonstrates the benefits of its use, among which are the properties against flu, dysentery, vaginitis, gastritis, besides having a calming effect (Braz et al., 2015; Messias et al., 2015; Lee et al., 2016). It has properties against genitourinary and intestinal infections; kidney and liver disorders, especially in the treatment of urinary system and kidney stones, with diuretic and analgesic factors; decreases the fixation of calcium oxalate in the renal walls and increases filtration through the glomeruli, causing relaxation of the ureter and excretion of uric acid, which facilitates the natural elimination of calculi (Cruces et al., 2013; Braz et al., 2015).

The use of the plant helps to fight inflammation and infections, has an anesthetic, antioxidant, antispasmodic, antilipolytic, anti-inflammatory, anti-hyperalgesic and antinociceptive character (Gorski et al., 1993; Venturi e Randi, 1997; Lorenzi e Matos, 2002; Nascimento, 2008; Aita et al., 2009; Marques, 2010; Oliveira et al., 2012; Lee et al., 2016; Escola de Saúde Pública, 2018; Oliveira et al., 2019). It has also been demonstrated as a potential anti-hepatitis B, anti-diabetes and also as antiplasmodial, antiviral and antimicrobial, including anti-caries activities, which can be used in products for oral use (Venturi e Randi, 1997; Lorenzi e Matos, 2002; Nascimento, 2008; Aita et al., 2009; Marques, 2010; Oliveira et al., 2012; Sunitha et al., 2017; Escola de Saúde Pública, 2018; Oliveira et al., 2019). The use of the *Phyllanthus niruri* L. plant as an infusion prevents the agglomeration of calcium oxalate, and also prevents the adhesion of crystals in the epithelium, decreasing the endocytosis process and consequently the formation of calculi. The species has a self-defense that regulates the passage of calcium in its cells, accumulating these particles in its leaves, and this natural self-defense is maintained in the aqueous extract of the herb when the infusion is prepared, promoting the antispasmodic action and anti-hyperuricemic effects, used as a methanolic extract also demonstrates a reduction in uric acid (Braz et al., 2015; Lee et al., 2016).

The wide use of *Phyllanthus niruri*, due to its widespread use and knowledge of its therapeutic characteristics, is scientifically studied in several regions, mainly in India and Brazil , and the lack of a pre-established protocol for the performance of all tests limits the comparisons between the results of research that occur worldwide with this species (Salomé, 2007; Lee et al., 2016; Escola de Saúde Pública, 2018). Based on the available literature, the species *P. niruri* is commonly used and has numerous biological activities, and data on sensitivity to *P. niruri* extract, as well as activity against microorganisms in planktonic state or biofilm, may increase knowledge about the use of extracts as an antimicrobial agent in the treatment of bacterial and fungal infections or as coadjuvants, along with enabling its pharmacological action as a pharmacological agent, and analyze the possible side effects.

## Conclusion

Through surveys carried out in this review, we may conclude that, researchs with medicinal plants, has been of great importance for the discovery of new compounds with antimicrobial properties. The understanding of these medicinal plants makes it necessary to know the mechanism of action by each component, when it comes in contact with the microorganism and thus, in this context, to be able to expand the options for the use of herbal medicines. The knowledge of the *Phillanthus niruri* and its applicability as antimicrobial agent cited in this review must be take in account by researches in this area of investigation according the avaiable methodologies to know more about these specie and its applicability as medicinal agent.

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