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Medicinal plants of the Unified Health System (Sistema Único de Saúde) with antifungal potential

Plantas medicinais do Sistema Único de Saúde com potencial antifúngico

Mônica Jachetti Maciel[1], *Claudete Rempel*[1], *Amanda Luisa Stroher*[1], *Patrícia Caye Bergmann*[1], *Diorge Jônatas Marmitt*[1]

ABSTRACT

Medicinal plants synthesize various secondary metabolites that can be used for therapeutic and antimicrobial purposes. In Brazil, the Unified Health System (SUS) offers several herbal medicines as an alternative in the treatment of various diseases. Considering the importance of these plants in the production of chemicals that expand therapeutic options and improve the health of SUS users, this review was carried out to quantitatively determine the antifungal activity of plants used as phytotherapeutics at RENAME. The selection of papers was performed at three distinct stages: examining and choosing titles related to antifungal action, reading the abstracts, and reading the whole selected articles. This review selected 22 studies of interest; 12 of them were conducted in Brazil and 10 were carried out in other countries. The papers chosen tested the growth inhibitory effect of plants against fungal species of agricultural and health importance, ranging from filamentous to yeast-like fungi, and *Candida albicans* was the most tested species. The growth of 39 fungal species were inhibited by some concentration of the extract used, with either an increase or decrease in antifungal activity depending on the extract used. The most frequently analyzed plant was the species *Schinus terebinthifolius* Raddi., studied in seven papers. The results found demonstrate the importance of analyzing medicinal plants and incorporating plant-based medicines in healthcare as an alternative source of treatment, highlighting the need for studies that evaluate the mechanisms action of their cytotoxicity and therapeutic effects in the human body.

Keywords: herbal medicines; fungi; secondary metabolites.

RESUMO

As plantas medicinais produzem uma série de metabólitos secundários que podem ser usados para fins terapêuticos e antimicrobianos. No Brasil, o SUS disponibiliza uma série de medicamentos fitoterápicos como alternativa ao tratamento de diversas enfermidades. Considerando a importância da utilização dessas plantas na produção de medicamentos que ampliem as opções terapêuticas e melhorem a atenção à saúde de usuários do sistema, elaborou-se este estudo de revisão com o objetivo de estimar quantitativamente a atividade antifúngica das plantas utilizadas como fitoterápicos contidas na RENAME. A seleção de artigos deu-se por meio de três etapas distintas: leitura e escolha de títulos relacionados à ação antifúngica, leitura dos resumos e leitura na íntegra dos artigos selecionados. Esta revisão selecionou 22 estudos de interesse, sendo 12 elaborados no Brasil e 10 em outros países. Os artigos escolhidos testaram a ação inibitória das plantas contra espécies de fungos de importância agrícola e sanitária, entre filamentosos e leveduriformes, sendo *Candida albicans* a espécie mais testada. Trinta e nove espécies foram inibidas por alguma concentração do extrato utilizado, havendo aumento ou diminuição da atividade antifúngica conforme substância extratora utilizada. A planta mais analisada foi a espécie *Schinus terebinthifolius* Raddi., estudada em sete artigos. Os resultados encontrados demonstram a importância da análise de plantas medicinais e da incorporação de medicamentos à base de plantas como fonte alternativa de tratamento, salientando a necessidade de estudos que demonstrem sua citotoxicidade e mecanismos de ação terapêutica no organismo humano.

Palavras-chave: medicamentos fitoterápicos; fungos; metabólitos secundários.

[1]Universidade do Vale do Taquari (Univates) – Lajeado (RS), Brazil.

Correspondence address: Mônica Jachetti Maciel – Avenida Avelino Talini, 171 – Bairro Universitário – CEP: 95914-014 – Lajeado (RS), Brazil. E-mail: monicajm@univates.br

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Introduction

the set of chemical reactions performed by plants produces a series of substances called secondary metabolites, which include flavonoids, tannins, alkaloids, saponins, coumarins and quinones, also encompassing the so-called essential oils or essences. These metabolites have various functions, which are related to the defense against animals, insects and other plants, protection from physical factors and attraction of animals for reproductive purposes (Simões et al., 2017; Tamariz-Angeles et al., 2018). In addition, many of these substances are important for characterizing and confirming the identity and quality of the plant in question, also manifesting antimicrobial activities, especially against bacteria, protozoa and fungi (Maciel et al., 2017).

Several studies have shown the beneficial use of extracts and active principles extracted from plants against pathogens that can infect and cause harm to animals, humans and plant crops (Chansue, 2007; Itako et al., 2009; Marmitt et al., 2015a; 2015b; Pinho et al., 2012; Rodrigues et al., 2007). New antimicrobial assets derived from natural sources can decrease the amount of pesticides and other chemical products for environmental control applied on farms, reducing the risks to our health and to the environment. Hence, they become a safer — and often more effective — alternative than pesticides (Mauli et al., 2009; Schwan-Estrada et al., 2000). they can also be an alternative to prevent many microorganisms from developing resistance to drugs used for their control, which increases the incidence of diseases caused by these pathogens and hampers the treatment of people affected (Cavalcanti et al., 2012; França et al., 2009; Maciel et al., 2017; Nogueira et al., 2008).

In 2009, the National List of Medicinal Plants of Interest to SUS (RENISUS) was established. Consisting of 71 plant species with therapeutic potential according to traditional medicine knowledge, with the purpose of promoting the study of herbal medicines and their production in Brazil (Brazil, 2009a; 2009b). The provision of plant-derived medicines by the Brazilian public healthcare system began in 2007 through the National List of Essential Medicines (RENAME) (Brazil, 2017b), and currently comprises 12 plants: *Aloe vera* (L.) Burm.f., *Cynara scolymus* L., *Glycine max* (L.) Merr., *Harpagophytum procumbens* (Burch.) DC. ex Meisn., *Maytenus ilicifolia* Mart. ex Reissek, *Mentha piperita* L., *Mikania glomerata* Spreng., *Plantago ovata* Forssk, *Rhamnus purshiana* DC., *Salix alba* L., *Schinus terebinthifolius* Raddi, and *Uncaria tomentosa* (Willd. ex Schult.) DC.; offered in the form of syrups, tablets, capsules, gels, creams and dyes (Brazil, 2012; 2017a; 2017b).

Considering the purpose for which RENISUS has been created, the aim of this systematic review was to show the amount of studies published on medicinal plants with antifungal activity as described in the national list of medicinal plants provided by SUS, using the CAPES (Coordination for the Improvement of Higher Education Personnel) Journals Portal as database, which encompasses publications from several other platforms, such as SciELo, PubMed and Springer, among others.

Materials and methods

The present study used a systematic review of the literature as a technical procedure for gathering scientific information encompassing different cases, locations and perspectives from different researchers, summarizing their objectives and results in a simplified manner (Greenhalgh, 1997; Carneiro; Takayanagui, 2009). The studies addressed here were those concerning the antifungal potential of medicinal plants provided as phytotherapeutics by SUS through RENISUS, and those with the full text available at the Capes Journals Portal in English, Portuguese or Spanish, were analyzed with no restrictions as to their publication year. Descriptors used were the scientific names of the plants (or phytotherapeutics) at RENAME and the term "antimicrobial", followed by the Boolean operator "and", with no restrictions of language or publication year.

The access link used was the one made available in the database. The titles of all the papers found when searching each species were read and the repeated ones were excluded, thus being counted only once. Review studies, interviews, reports, and studies on the practical use of plants or referring to their chemical constituents without either confirming or proving their antifungal effect were also excluded.

A total of 10,763 articles were found in the initial search; 382 were reports and 267 were repeated scientific papers, and they were thus excluded from the study. Of all articles found in the initial search, 417 studies were selected to comprise the further stages of this review. The publications chosen were analyzed in three stages: first, by reading the title of all articles found in the database, and selecting those that included terms related to antifungals, such as "fungos", "fungi", "levedura", "yeast", "*Aspergillus*", "*Candida*", "*Penicillium*", "*Fusarium*" and "antifúngico", among others. A total of 67 studies were selected. Afterwards, the next stage consisted of reading the abstracts of the papers selected in the first stage, which resulted in 32 papers selected. Those that somehow mentioned the method used and proved the antifungal effect of the studied plant were chosen. In the third and last stage, the papers selected in the second phase were completely read, to prove the antifungal effect of the plants of interest, and 22 studies were found to be compatible with the criteria established here, and were thus chosen to be included in the present review. The scientific names of the plants mentioned were written according to updated references for native plants in Brazil (Reflora, 2010) and introduced plants (Taxonomic Name Resolution Service, 2020).

During the search, a methodological adjustment was required to include the plant *Glycine max*. While using the same procedure adopted for the other plants, it was not possible to read the papers available starting on page 281 due to problems in the platform used for the search. To complete the search for this plant, restricting the publication year to 2009, the year in which RENISUS was created, was required. Only with this adjustment, was it possible to access all the studies published as of this date and the search for this descriptor was not complete.

Results and Discussion

After reading the 32 selected papers completely, 22 studies of interest were selected for inclusion in the present review, which corresponds to 5.3% of the total relevant papers initially found in the database. Chart 1 shows the total number of papers selected for each study of interest of each plant analyzed, followed by methodology and main results.

Of the 12 plants that comprised this study, no studies on *Maytenus ilicifolia*, *Salix alba* and *Rhamnus purshiana* were selected, due to the fact that none of the papers found met the selection criteria. The papers were organized in a distribution chart by antifungal potential and therapeutic action (Chart 1). There were three publications in 2011, which was the year with the highest number of publications. The most recent research among the papers selected was from 2017, and the oldest was from 2002.

Of the 22 selected studies, 12 (54.5% of the total) were conducted by Brazilian researchers (Biasi-Garbin et al., 2016; Braga et al., 2007; Duarte et al., 2005; Freire et al., 2012; Holetz et al., 2002; Johann et al., 2008; Martinelli et al., 2017; Moraes et al., 2015; Moura-Costa et al., 2012; Schmourlo et al., 2005; Santos et al., 2010; Souza Júnior et al., 2011), which indicates that the creation of RENISUS did promote medicinal plant studies in Brazil.

Reports indicate that medicinal plants were already used in Europe in 460 B.C. in the form of hot and iced teas, moist compresses and dried herbs. They are still used today by many European countries as complementary medicines in the treatment of many diseases. Several other cultures have also relied on the properties of medicinal plants for thousands of years, with several species still in use to date (Van Wyk; Wink, 2018). Of the 22 selected articles in this study, nine (41%) were carried out in other countries, especially India and Iran, with two studies each. The most tested plants in these studies were *Mentha piperita*, with 6 studies, and *Cynara scolymus*, with 2 studies.

In the international scenario, studies on medicinal plants, especially those focused on public health systems, have been disseminated since the First International Conference on Primary Health Care, held in 1978 in Russia (Gonçalves et al., 2017). Heinrich (2010), studying medicinal plants worldwide, indicated an increase in the search for phytotherapeutics for the treatment of AIDS/HIV and viral diseases. In the same study, he points out that research has focused on the innovation of phytochemical studies for the isolation and identification of active ingredients. Since 1979, the World Health Organization has suggested the inclusion of complementary alternative medicine therapies in public health policies, with their use reaching 75% in France, 70% in Canada, and 42% in the USA (Zeni et al., 2017).

Estimates indicate that 70–80% of drug development depends exclusively on plants, and much of the research in this area is focused on the isolation of plant active ingredients (Aslam; Ahmad, 2016). According to Rajeswara Rao and Rajput (2010), the major research areas on medicinal plants in the world are: development of technologies for the cultivation and isolation of chemical compounds, implementation of quality control protocols, scientific validation of the traditional use of these plants, development of products using them as a production base, selection of markers for genotypes, creation of a DNA profile of the species studied, identification and isolation of enzymes and bioactive molecules, and screening of phytochemical compounds with antimicrobial properties.

The nine international studies selected for this review were *in vitro* and 66.7% (6) also analyzed the chemical compounds present in the study plant, using chromatographic methods. None of them, however, identified the specific compound accounting for the antifungal activity observed.

Of the international studies selected, seven (77.8%) were carried out after 2010, one of which was published in 2019. Compared to the Brazilian studies, where 58.3% were published in or after 2010, there was an increase in studies in this area at the global level after this period. In a comparative study, Assis et al. (2015) showed a strong growth trend in research on medicinal plants in analyzing 111 research groups between 1997 and 2010, a trend that has continued to intensify in later years.

It is known that most medicinal plants are available in tropical countries (Dar et al., 2017). India and Iran stood out as the countries with the highest number of papers of interest, with two studies each (Desam et al., 2019; Tyagi; Malik, 2011; Saharkhiz et al., 2012; Mahboubi; Kazempour, 2014), having an important diversity of plants relevant to the healthcare area (Panda et al., 2018; Tandon; Yadav, 2017; Sadat-Hosseini et al., 2017; Parsaei et al., 2016).

The pharmacology of natural products allows determination of the bioactive compounds present in plants, that are responsible for growth-inhibitory effects. These bioactive compounds, also called secondary metabolites, have antimicrobial effects due to their cytotoxicity, and because of their neuroactive effects, they can be used as analgesics, anesthetics and antidepressants, among others (Vizzotto et al., 2010). As indicated by Piriz et al. (2014), medicinal plants have several beneficial properties that can be used for the benefit of humans. In their study, Piriz et al. (2014) found relevant results of studies on anti-inflammatory activity, especially in Brazil, which was the country with the highest number of papers published. The same number of papers produced in Brazil (12) was found in the present study, showing the importance and competence of Brazilian research demonstrated in this area.

Marmitt et al. (2015b), in a review, searched for plants with antibacterial effect in RENISUS, and found that 42% of the 19 selected published studies of interest were conducted in Brazil, thus indicating an increase in studies in the country after the creation of the National Policy on Medicinal and Herbal Plants (PNPMF). Similar results were found in the present study: of the 13 studies carried out in Brazil, 69% (9) were published after the creation of PNPMF. PNPMF (Brazil, 2006) has contributed to the increase in research aimed at the development of new plant-derived drugs, which are already used popularly in conventional medicine.

Chart 1 – Antifungal potential and therapeutic action of medicinal plants evaluated in the studies of interest selected.

Plant species (Family)	Part of the plant / compound / concentration used / treatment regimen (dose)	Therapeutic activity	Type of study	Year of publication/ Journal/ Country
Aloe Vera (Xanthorrhoeaceae)	Gel from the mucilaginous part of the leaf plus potato dextrose agar (PDA) / Concentrations of 1, 5, 25, 50, and 100 mL/L	Growth-inhibitory activity was detected at the lowest concentrations of the gel, which was effective against the fungi *Penicillium digitatum* and *Botrytis cinerea*	In vitro	2010/ *Postharvest Biology and Technology*/ Spain
Cynara scolymus (Asteraceae)	Chloroform, ethyl acetate and butanol extract of dry leaves / Doses of 2.5, 5 and 10 mg/mL	The butanol extract exhibited higher growth-inhibitory activity and was the only one capable of preventing the growth of *Candida lusitaniae* and *Mucor mucedo*	In vitro	2004/ *Journal of Agricultural and Food Chemistry*/ China
Cynara scolymus (Asteraceae)	Extract of powder from dry leaves with ethanol at the concentrations 25, 50, 75 and 97% v/v, 50% methanol, and pure water / Concentrations from 2.5 to 20 mg/mL	The 75 and 97% ethanol extracts proved to have the highest activity against strains of *Candida albicans Candida* sp.	In vitro	2011/ *Tropical Journal of Pharmaceutical Research*/ Romania
Mentha piperita (Lamiaceae)	40 g of fresh plant parts to obtain the essential oil, using 50 mL of dichloromethane for extraction / Dose of 2–0.03 mg/mL	It showed moderate activity (MIC of 0.6 mg/mL) in the control of *Candida albicans* strains	In vitro	2005/ *Journal of Ethnopharmacology*/ Brazil
Mentha piperita (Lamiaceae)	Dried seed extract obtained using 95% ethanol / Concentrations of 50, 25, 12.5, and 6.25 mg/mL / Dose 1 mg/mL	The extract could inhibit *Aspergillus niger* and *Candida albicans* with MIC of 5 mg/mL	In vitro	2006/ *Biology*/ Turkey
Mentha piperita (Lamiaceae)	Hydrodistilled extract of leaves (1:7 w / v), extracted using dichloromethane (5:1 v/v) / Concentration 0.1-0.2% (v/v)	The essential oil inhibited the growth of *Aspergillus flavus, Aspergillus glaucus, Aspergillus niger, Aspergillus ochraceous, Colletotrichum gloeosporioides, Colletotrichum musae, Fusarium oxysporum*, and *Fusarium semitectum*	In vitro	2011/ *Journal of Food Safety*/ Brazil
Mentha piperita (Lamiaceae)	Essential oil extracted using ethanol and diethyl ether / Concentrations of 0.14–18 mg/mL / Doses of 10–40 µL	The extract was effective against *Aspergillus flavus, Aspergillus niger, Mucor spp., Fusarium oxysporum, Candida albicans*, and *Saccharomyces cerevisiae*, and its highest efficacy was against *Penicillium digitatum*	In vitro	2011/ *Food Control*/ India
Mentha piperita (Lamiaceae)	Hydrodistillation of aerial parts during flowering / at 1:50 and 1:1,000 dilutions	The oil could inhibit *Cryptococcus neoformans, Aspergillus flavus, Aspergillus fumigatus, Aspergillus oryzae, Aspergillus clavatus*. It also completely inhibited biofilm formation by *Candida albicans* and *Candida dubliniensis*	In vitro	2012/ *International Scholarly Research Network*/ Iran
Mentha piperita (Lamiaceae)	Extraction of essential oil by hydrodistillation of the aerial parts of the plant at the beginning of flowering / Concentrations of 16–0.25 µg/mL	The oil exhibited antimicrobial activity against strains of *Candida albicans, Candida glabrata*, and *Aspergillus niger*	In vitro	2014/ *Songklanakarin Journal of Science and Technology*/ Iran

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Chart 1 – Continuation.

Plant species (Family)	Part of the plant / compound / concentration used / treatment regimen (dose)	Therapeutic activity	Type of study	Year of publication/ Journal/ Country
Mentha piperita (Lamiaceae)	Hydrodistillation of dry leaves to obtain the extract dissolved in 95% ethanol / Concentrations of 4, 2, 1, 0.5, 0.25, 0.125 µL/mL	It prevented the growth of *Microsporum canis, Epidermophyton floccosum, Trichophyton rubrum*, and *Trichophyton mentagrophytes* at concentrations of 2.0 and 4.0 µL/mL	In vitro	2015/ *Environmental Health and Preventive Medicine*/ Egypt
Mentha piperita (Lamiaceae)	Hydrodistillation at 1:5 concentration / dose of 1 µL	The essential oil exhibited strong antifungal activity against *Alternaria, Penicillium* spp., *Fusarium oxysporum, Fusarium tabacinum, Aspergillus fumigatus, Candida albicans, Cladosporium herbarum*, and *Rhizoctonia solani*	In vitro	2017/ *Journal of King Saud University*/ India
Mikania glomerata (Asteraceae)	Lower parts of the plant were macerated with water and ethanol (90–10%) / Dose of 2 mg/mL	It exhibited moderate activity (MIC of 100–500 µg/mL) against *Candida krusei* and *Candida parapsilosis*	In vitro	2002/ *Memórias do Instituto Oswaldo Cruz*/ Brazil
Mikania glomerata (Asteraceae)	40 g of fresh parts of the plant were used to obtain the essential oil, using 50 mL of dichloromethane for extraction / Dose of 2-0.03 mg/mL	It exhibited weak inhibitory activity (MIC > 2.0 mg/mL) compared to *Candida albicans*	In vitro	2005/ *Journal of Ethnopharmacology*/ Brazil
Schinus terebinthifolius (Anacardiaceae)	Aqueous-ethanol extract (20:3 mg/mL) from the aerial parts / Concentration of 1 mg/mL	The aqueous extract was able to prevent the growth of *Candida albicans*	In vitro	2005/ *Journal of Ethnopharmacology*/ Brazil
Schinus terebinthifolius (Anacardiaceae)	Methanol extract (3:2,000) / Dose of 100 mg/mL	It exhibited antifungal activity against *Candida albicans* and *Cryptococcus neoformans*	In vitro	2007/ *Journal of Ethnopharmacology*/ Brazil
Schinus terebinthifolius (Anacardiaceae)	Oil extraction from leaves with 80% ethanol and addition of water, hexane, dichloromethane and ethyl acetate / Concentrations from 1,000 to 7.8 µg/mL	The ethyl acetate extract portion exhibited higher antifungal activity against strains of *Candida albicans*	In vitro	2008/ *World Journal of Microbiology and Biotechnology*/ Brazil
Schinus terebinthifolius (Anacardiaceae)	Extract obtained by hydrodistillation / Concentrations of 25, 50, 75 and 100% / Dose of 100 µL/mL	The 25% dilution was able to inhibit the growth of *Colletotrichum* sp., *Alternaria* spp. and *Botrytis* spp. *Fusarium* spp. was only inhibited by the 50% dilution	In vitro	2010/*Revista Brasileira de Farmacognosia*/ Brazil
Schinus terebinthifolius (Anacardiaceae)	Hydroalcoholic extract of the bark (1:10) / Dose of 2 mg/mL	It exhibited inhibitory activity against strains of *Candida tropicalis* and *Candida parapsilosis*	In vitro	2012/ *Journal of Ethnopharmacology*/ Brazil
Schinus terebinthifolius (Anacardiaceae)	Aqueous, ethanol and acetone extracts / Concentrations from 1,000 to 1.95 µg/mL / Dose of 2,000 µg/mL	Ethanol extract exhibited strong activity against *Trichophyton rubrum* and *Trichophyton mentagrophytes*	In vitro	2016/*Revista do Instituto de Medicina Tropical de São Paulo*/ Brazil

Continue...

Chart 1 – Continuation.

Plant species (Family)	Part of the plant / compound / concentration used / treatment regimen (dose)	Therapeutic activity	Type of study	Year of publication/ Journal/ Country
Schinus terebinthifolius (Anacardiaceae)	Dichloromethane and oleoresin extract / Concentrations of 1–0.05%	Oleoresin and the extract exhibited moderate activity against strains of *Candida albicans* and *Penicillium* sp.	In vitro	2017/ *Ciência Rural*/ Brazil
Uncaria tomentosa (Rubiaceae)	Hydroalcoholic extract 70% of the stem in a 1:1 ratio / Concentrations at 1:512 dilution	It exhibited strong activity against the strains of *Candida albicans*, *Candida krusei*, *Candida tropicalis*, *Candida guilliermondii* up to 1:16 dilution	In vitro	2011/ *Pesquisa Brasileira em Odontopediatria e Clínica Integrada*/ Brazil
Uncaria tomentosa (Rubiaceae)	Hydroethanolic extract (50% v/v) / Concentration of 1 mg/mL	It exhibited strong activity against the resistant species *Candida krusei* and *Candida glabrata*	In vitro	2015/ *Industrial Crops and Products*/ Brazil

Source: Castillo et al. (2010), Ertürk (2006), Ibrahim and El-Salam (2015), Vamanu et al. (2011) and Zhu et al. (2004).

Different numbers of papers were found for each plant species selected, indicating a variety and effectiveness of different mechanisms of action in each species. The therapeutic activity shown is related to the extraction method and dose used. Extraction using aqueous-ethanol solvents afforded higher growth-inhibitory activity (27 different strains growth-inhibited), followed by extraction of essential oils using hydrodistillation (22 different strains growth-inhibited) and extraction using dichloromethane (12 different strains growth-inhibited). Different solvents extract different active principles from the plant, which are responsible for the effects caused by the use of medicines containing these substances (e.g., anti-inflammatory, hypoglycemic, anticoagulant and antiplatelet activities) (Sixel; Pecinalli, 2005).

Studies show that the use of the crude extract, shows a considerably higher bioactivity than using each active principle separately (Sixel; Pecinalli, 2005). The studies analyzed in this review, therefore, showed higher antimicrobial activity, since all the assays were performed using crude extracts. Among all the plants analyzed, approximately 54% (12) showed growth-inhibition in all of the fungal species tested, and 41% (9) at least prevented the growth of 50% of the species analyzed. The butanol extract of *Schinus terebinthifolius* was tested against *Candida neoformans*, *Candida albicans*, and *Trychophyton rubrum*, and inhibited only *Candida albicans* strains.

Analyzing the data obtained, *Candida albicans* was the most tested microorganism in all papers selected, totaling 16 studies analyzing extracts and oils against strains of this species. Overall, 18 studies (78.3% of the total) analyzed seven *Candida* species regarding their sensitivity to medicinal plant extracts and oils. Filamentous fungi were also part of the selected studies. Nine species of *Aspergillus* were used in seven articles (39.2% of the total), and *Aspergillus niger* was most studied, appearing in six papers.

According to Correia et al. (2006), the family Anacardiaceae is rich in bioactive compounds that may have antimicrobial effects, with the genus *Schinus* being among the 11 most studied in this family. Correia et al. (2006) demonstrated the presence of phenolic lipids in this plant. These compounds have amphipathic characteristics, which facilitate their penetration into the plasma membrane, causing changes in their structure and properties. Therefore, seven of the 22 studies selected for this review analyzed the bioactive and antimicrobial activity of *Schinus terebinthifolius*, which prevented the growth of 78% (14) of the 18 strains tested.

Another important factor, pointed out by Gobbo-Neto and Lopes (2007), indicates that changes in the concentrations of active compounds may occur due to circadian cycle (day/night), seasonality, plant age, development period, temperature, attack by pathogens, pollution, and the hormonal development process in the plant. Evans (2009) showed significant differences in the presence of chemical compounds during winter and summer. Vasconcelos Silva et al. (1999) demonstrated how the circadian cycle affects the production and concentration of bioactive substances, showing high quantitative contrasts at different times of the day.

Stress caused by temperature variations can also affect the concentrations of these compounds, as indicated by Christie et al. (1994). Plant age is also related to these changes. Flowering period leads to increase or decrease in certain substances, as well as the period of leaf emergence or loss in deciduous plants. This indicates why the same plant species had different results in this paper. Two studies carried out with *Mentha piperita* (Mahboubi; Kazempour, 2014) (Saharkhiz et al., 2012) used *Aspergillus flavus* samples to test the antimicrobial action of essential oils extracted using hydrodistillation. The first study used the aerial parts at the beginning of flowering to obtain essential oils and observed excellent growth-inhibitory activity. However, the second study, which also used aerial parts to extract essential oils, although after the beginning of flowering, found no growth-inhibitory action at any concentration in *Aspergillus flavus* strains.

The same occurred in studies carried out by Schmourlo et al. (2005) and Biasi-Garbin et al. (2016), who tested the action of the ethanol extract of the species *Schinus terebinthifolius*. The extract was prepared using different parts of the plant in each study, differing only in the concentration used (Chart 1). At the end of the study, Biasi-Garbin et al. (2016) were able to inhibit the growth of the pathogenic fungus *Trichophyton rubrum*, while Schmourlo et al. (2005) showed no effect on this fungus. Schmourlo et al. (2005) and Braga et al. (2007) conducted a study with the same plant species using extracts against *Candida neoformans* strains. Alcoholic extracts were obtained for both studies; Schmourlo et al. (2005) used ethanol as extraction solvent and Braga et al. (2007) used methanol. In the first study, the extract did not prevent the growth of *Candida neoformans*, while it was inhibited in the second study, thus indicating that different solvents affect the composition of bioactive substances, either intensifying or preventing the effect of the extract, as already observed by Silva (2010). Silva (2010) compared different extracts of essential oils, classifying the different activities exhibited by each extract. Thus, he identified significant differences in the action of different solvents, related to solubility and affinity with the plasma membrane of the strains he compared.

Conclusion

Of the 417 papers initially read, 22 that demonstrated an antifungal effect were selected for the present review. The two plants that exhibited the highest antifungal activity were *Mentha piperita*, with eight studies, and *Schinus terebinthifolius*, with seven studies. *Candida albicans* was the most frequently tested fungal species, as it was present in 11 different studies. Other species of the genus *Candida* were tested in 10 different studies. The genera *Fusarium* and *Aspergillus* also stood out, with five and 13 studies, respectively.

The incorporation of integrative and complementary practices within the scope of SUS through PNPMF helps to understand and perceive the importance of studies on this topic. RENAME has also played an important role in the increase and constant evolution of the research on herbal medicines in Brazil, especially after their inclusion in SUS.

There is a therapeutic equivalence between essential oils and extracts used to obtain active ingredients. Thus, the importance of evaluating these compounds for cytotoxicity, bioavailability and therapeutic action in humans is evident to ensure that they can be used as drugs, having proven their extensive activity against microorganisms.

Contribution of authors:

Maciel, M. J.: Supervision, Funding Acquisition, Formal Analysis, Writing, Review & Editing. Rempel, C.: Supervision, Funding Acquisition, Formal Analysis, Writing, Review & Editing. Stroher, A. L.: Methodology, Investigation, Data Curation, Writing. Bergmann, P. C.: Methodology; Investigation, Data Curation, Writing. Marmitt, D. J.: Supervision, Formal Analysis, Writing, Review & Editing.

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