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Review

Anti-*Sporothrix* spp. activity of medicinal plants

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Cases of sporotrichosis in humans and animals without satisfactory clinical response have increased, a warning sign of strains resistant to conventional antifungal agents. The urgent search for alternative therapies was an incentive for research on medicinal plants with anti-*Sporothrix* spp. properties. A bibliographic survey was performed based on scientific papers about *in vitro* and *in vivo* antifungal activity of essential oils and extracts of plants in differents solvents against the fungal of the *Sporothrix schenckii* complex. The study methodology consisted of a literature review in *Google Scholar, Science Direct, Pubmed, Bireme* and *Springer link* with papers from 1986 to 2015. We found 141 species of plants that were investigated, of which 100 species were concentrated in 39 botanical families that had confirmed anti-*Sporothrix* activity. Combretaceae, Asteraceae and Lamiaceae represented the botanical families with the greatest number of plants species with antifungal potential, using different methodologies. However, there are few studies with medicinal plants in experimental infection in animals that prove their activity in the treatment of sporotrichosis. It reinforces the need for further research related to standardization of *in vitro* methodologies and *in vivo* studies related to safety and to toxicity potential of these plants with anti-*Sporothrix* spp. activity.

Uniterms: *Sporothrix schenckii* complex. Antifungals. Combretaceae/pharmacognosy. Asteraceae/pharmacognosy. Lamiaceae/pharmacognosy. Medicinal plants/antifungal activity.

Casos de esporotricose em humanos e animais sem resposta clínica satisfatória têm aumentado, sinal de alarme para o surgimento de cepas resistentes aos antifúngicos convencionais. A urgente busca por alternativas terapêuticas tem incentivado as pesquisas em plantas medicinais com atividade anti-*Sporothrix* spp. Um levantamento bibliográfico foi realizado com base em artigos científicos sobre a atividade antifúngica *in vitro* e *in vivo* de óleos essenciais e extratos de plantas preparados em diferentes solventes contra o complexo *Sporothrix schenckii*. A metodologia do estudo consistiu em uma revisão bibliográfica em *Google Scholar, Science Direct, Pubmed, Bireme* e *Springer link* com artigos desde 1986 até 2015. Foram encontradas 141 espécies de plantas já investigadas, das quais 100 espécies concentradas em 39 famílias botânicas apresentaram atividade anti-*Sporothrix* spp. confirmada. Combretaceae, Asteraceae e Lamiaceae representaram as famílias botânicas com maior número de espécies vegetais com potencial antifúngico, empregando diferentes metodologias. Entretanto, há poucos estudos com plantas medicinais em infecção experimental animal comprovando sua atividade no tratamento da esporotricose. Reforça-se a necessidade de mais pesquisas relacionadas à padronização de metodologias *in vitro* e a estudos *in vivo* relacionados à segurança e potencial tóxico dessas plantas com atividade anti-*Sporothrix* spp.

Unitermos: *Sporothrix schenckii*. Antifúngicos. Combretaceae/farmacognosia. Asteraceae/farmacognosia. Lamiaceae/farmacognosia. Plantas medicinais/atividade antifúngica.

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INTRODUCTION

Among the diseases with zoonotic potential, sporotrichosis is recognized as an emerging mycosis with worldwide occurrence that tends to increase exponentially in the number of cases in domestic animals and humans and is considered a neglected epidemic in the state of Rio de Janeiro, Brazil (Schubach, Barros, Wanke, 2008; Barros *et al.*, 2010; Silva *et al.*, 2012; Rodrigues *et al.,* 2013). This disease is the most common subcutaneous mycosis in the Americas, especially in Brazil, Mexico, Colombia and Peru, and also occurs in South Africa, India and Japan (Carrada-Bravo, Olvera-Macías, 2013). The sources of environmental fungus infection include soil, decomposed vegetation, tree stems, and other elements. The infection may also occur through bites and scratches of cats that may carry *Sporothrix* spp. conidia and, through inoculation, transmit the fungal agent into the dermis (Larsson, 2011; Romeo, Criseo, 2013). Although the treatment with antifungal drugs is effective, *in vitro* studies acknowleded the emergence of strains of *Sporothrix* spp. resistant to antifungals (Meinerz *et al.*, 2007; Marimon *et al*., 2008; Rodrigues *et al.*, 2013; Stopiglia *et al.*, 2014).

There is a continuing and urgent need to discover new antifungal compounds and to understand their mechanisms of action (Kontoyiannis, Lewis, 2002; Cleff *et al.*, 2008; Gaitán *et al.* 2011). It is known that the use of plants and derivatives for medicinal purposes is an ancient practice used worldwide, primarily in Eastern cultures, and is utilized by up to 80% of the population of developing countries and has been increasingly used in the West, according to data from the World Health Organization in the 1990's (Veiga Jr., Pinto, 2005).

Faced with resistant cases of sporotrichosis, the search for alternative therapies in their treatment has increasingly been conducted by several international researchers, whose papers reveal the potential anti-*Sporothrix* spp. of certain medicinal plants (Rojas *et al.*, 2003; Masoko, Picard, Eloff, 2007; Cleff *et al*., 2008; Suleiman *et al.*, 2009; Johann *et al.*, 2011; Joshi *et al.*, 2011; Stopiglia *et al.*, 2011). However, there is a lack of standardization of tests with medicinal plants and this makes the comparison of antifungal activity of the plants difficult. Thus, this review aimed for a new approach of sporotrichosis and grouped the studies in the medicinal plants with anti-*Sporothrix* spp. activity according to the methodology for antifungal evaluation. A bibliographic survey was performed based on scientific papers researched in *Google Scholar, Science Direct, Pubmed, Bireme* and *Springer link* and papers from 1986 to 2015 were evaluated.

SPOROTRICHOSIS AND ITS CONVENTIONAL THERAPY

Chronic or subacute, the clinical manifestations of sporotrichosis occur in dependence of the host immune status, commonly resulting in limited damage to the dermis, with or without involvement of the lymphatic system in humans and animals, which can produce subcutaneous nodules, and may also produce manifestations in the respiratory system, such as dyspnea, nasal discharge and sneezing (Schubach, Barros, Wanke, 2008; Barros *et al.*, 2010; Madrid *et al.*, 2012).

The conventional therapy for sporotrichosis includes the use of antifungal agents such as potassium iodide, itraconazole, ketoconazole, amphotericin B and terbinafine, among others, as well as the adoption of local thermal therapy and the surgical excision of the lesion (Meinerz *et al.*, 2008; Gremião *et al.*, 2009; Honse *et al.*, 2010; Pereira *et al.*, 2011; Gremião *et al.*, 2011; Reis *et al.*, 2012). The preferred antifungal therapy for cat and dogs with sporotrichosis has been itraconazole administered daily orally at the dose of 10 to 40 mg kg^{-1} for a minimum period of three months and up to one year with no apparent adverse effects (Madrid *et al.*, 2010; Larsson, 2011; Rossi *et al.*, 2013). However, poor clinical response has been observed in cats with sporotrichosis (Gremião *et al.*, 2011).

The daily use of potassium iodide in capsules at dose of 2.5 to 20 mg kg^{-1} has provided clinical cure, although side effects may occur, as appetite loss and clinical signs of hepatotoxicity (Reis *et al.*, 2012). The association of subcutaneous amphotericin B with oral itraconazole is also an alternative in cats with sporotrichosis refractory to itraconazole (Gremião *et al.*, 2011). Furthermore, the association of itraconazole with (1-3) β-glucan promoted the case resolution after four weekly applications of glucan in a canine with refractory sporotrichosis to itraconazole by *Sporothrix brasiliensis* and it may be considered a promising alternative in cases of resistance to conventional therapy (Guterres *et al.*, 2014). In humans, the recommended the daily dosage of 100 up to 400 mg kg^{-1} of itraconazole has been succesfully used in a study with 645 patients, which the recovery rate was 94.6% (Barros *et al.*, 2010).

Experimental models in rats showed better activity of terbinafine (250 mg kg^{-1}) compared to itraconazole (100 mg kg^{-1}) in treatment of systemic sporotrichosis (Meinerz *et al.*, 2008), but in the cutaneous sporotrichosis, terbinafine (20 e 30 mg kg^{-1}) has shown little efficacy while itraconazole (10 mg kg^{-1}) showed good results (Antunes *et al.*, 2009). In human isolates of *S. schenckii, S. brasiliensis* and *S. globosa*, terbinafine had better *in*

vitro antifungal activity, followed by ketoconazole and fluconazole (Stopiglia *et al.*, 2014).

The therapeutic protocol adopted must be associated with clinical monitoring of the patient, especially in felines because they are sensitive to many medications (Nobre *et al.*, 2002; Madrid *et al.*, 2012). Toxic effects has been cited in cats and dogs treated with azoles, such as anorexia, emesis and hepatotoxic signs, as well as lethal cases in cats treated with saturated sodium solutions or 20% potassium iodide (Larsson, 2011).

The difficulties in obtaining therapeutical success can be associated with treatment time and the high cost of drugs that has been discouraging to the animals´ owners, who often abandon the therapy. These factors coupled with the indiscriminate use of antifungal drugs contributed to the problem of antifungal resistance (Schubach *et al.*, 2004; Marimon *et al.*, 2008; Rodrigues *et al*., 2013). Unfortunately, *in vitro* studies showed the emergence of *Sporothrix* spp. resistant to antifungals, including itraconazole, which is used as the preferred therapy in sporotrichosis (Marimon *et al*., 2008; Rodrigues *et al.*, 2013; Stopiglia *et al.*, 2014).

The difficulties observed in the therapeutical cure in human and animals show that the current situation calls for new therapeutic alternatives and/or new complements to conventional antifungal therapy. It is know that medicinal plants present antimicrobial properties which have been increasingly reported in international studies and it is expected that plant extracts have different target sites than used by currently available antimicrobials in being effective against drug-resistant microbial pathogens (Gibbons, 2003), including resistant strains of *Sporothrix* spp.

Currently, the agent of sporotrichosis has been reclassified and related to several species of *Sporothrix schenckii* complex, such as *S. brasiliensis, S. globosa, S. mexicana, S. albicans, S. inflata, S. schenckii* var. *luriei* and *S. schenckii* var. *schenckii*; which are identified only by molecular biology techniques (Marimon *et al.*, 2007). However, the studies on medicinal plants found in this review were only conducted with isolates of *S. schenckii* because this agent was, at the time, the only species identified in cases of sporotrichosis, since the genre had not yet been classified as *Sporothrix schenckii* complex.

PLANTS WITH ANTI-*SPOROTHRIX* SPP. POTENTIAL

Among the first reports of the search of plants with possible antifungal activity against *S. schenckii*, Minami and Oliveira (1986) studied alcoholic extract at 30% of *Bidens pilosa* (Compositae), a plant distributed in America, Asia and Africa, and they found no inhibitory antifungal activity. Fortunately, studies in the years following detected satisfactory *in vitro* activity of other plant species tested in different extracts types, concentrations and methodologies (Sinha, Gulati, 1990; Apisariyakul, Vanittanakom, Buddhasukh, 1995; Verástegui *et al.*, 1996; Saikia *et al.*, 2001; Rojas *et al.*, 2003; Masoko, Picard, Eloff, 2005; Luqman *et al.*, 2007; Damián-Badillo *et al.*, 2008).

According to the queried data, 141 species of plants have been subjected to *in vitro* tests against *S. schenckii,* and anti-*Sporothrix* spp. activity was conferred in 100 species belonging to 39 botanical families, in which were highlighted the families of Combretaceae (31% - 31/100) (Masoko, Picard, Eloff, 2005; 2007; Suleiman *et al.*, 2009), Asteraceae (11% - 11/100) (Rojas *et al.*, 2003; Damián-Badillo *et al.*, 2008; Salomão *et al.*, 2008; Stopiglia *et al.*, 2011) and Lamiaceae (7% - 07/100) (Sinha, Gulati, 1990; Luqman *et al.*, 2007; Fernández, 2005; Cleff *et al.*, 2008; Couto *et al*., 2015), which have the largest number of species with confirmed activity of interest. From the *in vitro* studies revised, a total of 233 extract products showed anti-*Sporothrix* spp. activity. The botanical information according to the consulted references is described in Table I.

IN VITRO SUSCEPTIBILITY TESTS

In the studies reviewed, the methodology utilized for research on plants were agar diffusion (Apisariyakul *et al.*, 1995; Saikia *et al.*, 2001; Rojas *et al.*, 2003; Luqman *et al.*, 2007; Damián-Badillo *et al.*, 2008; Verástegui *et al.*, 2008; Fatima *et al.*, 2009; Márquez, 2010; Joshi *et al.*, 2011), broth microdilution technique (Sinha, Gulati, 1990; Verástegui *et al.*, 1996; Johann *et al.*, 2007; Luqman *et al.*, 2007; Cleff *et al*., 2008; Fatima *et al.*, 2009; Johann *et al.*, 2009, 2011; Joshi *et al.*, 2011), bioautographic assay (Betina, 1973; Johann *et al.*, 2007; 2011), serial microdilution at 24 and 48 hours (Masoko, Picard, Eloff, 2005; 2007; Suleiman *et al.*, 2009) and agar cup method (Salomão *et al.*, 2008).

In the various methodologies utilized in the references, variation was observed in the values of concentration tested in extracts, making it difficult to compare the results and, thus, the designation of those plants with high, medium and low anti-*Sporothrix* spp. activity was not performed. According to Fennel *et al*. (2004), the lack of standardized methods for antimicrobial tests with natural products results in variations of minimum inhibitory concentration values. In addition,

TABLE I - Medicinal plants with confirmed anti-*Sporothrix* spp. activity and their taxonomical and anatomical identifications, extract types and the country where the study was conducted by the consulted references

Botanical Family	Plant Species	Plant Parts	Extract	Country	Reference
Agavaceae	*Agave lecheguilla*	Root	E	Mexico	Verástegui *et al.,*1996; 2008
		Leaves	E	Mexico	Verastegui *et al*., 2008
Agavaceae	*Agave lophantha*	Leaves	E	Mexico	Verastegui *et al.*, 2008
Agavaceae	*Agave picta*	Leaves	E	Mexico	Verastegui *et al.*, 2008
Agavaceae	*Agave scabra*	Leaves	E	Mexico	Verastegui *et al.*, 2008
Anacardiaceae	*Schinus terebinthifolius*	Leaves, Stems	Di, E, EA, He	Brazil	Johann *et al*., 2007
Anacardiaceae	*Loxostylis alata*	Leaves	Ac, Aq, Bu, Ch, CT Di, He, Ch, M	South Africa, Nigeria	Suleiman *et al.*, 2009; Suleiman, Naidoo, Eloff, 2012
Anacardiaceae	*Protorhus longifolia*	Leaves	Ac, Di, He, M	South Africa, Nigeria	Suleiman *et al.*, 2009
Apiaceae	*Cuminum cyminum*	Seed	Aq, EO, Ha, M	India	Chaudhary, Husain, Ali, 2014
Araucariaceae	*Araucaria* spp.	Resin	E	Brazil	Salomão *et al.*, 2008
Asteraceae	*Artemisia ludoviciana*	Leaves, Root, Flowers	Aq, EA, MC	Mexico	Damián-Badillo *et al.*, 2008
Asteraceae	*Heliopsis longipes*	Leaves, Root, Flowers	Aq, EA, MC	Mexico	Damián-Badillo *et al.*, 2008
Asteraceae	*Tagetes lucida*	Leaves, Root, Flowers	Aq, EA, MC	Mexico	Damián-Badillo *et al.*, 2008
Asteraceae	*Baccharis dracunculifolia*	Resin	E	Brazil	Salomão *et al.*, 2008
Asteraceae	*Ophryosporus peruvianus*	Leaves, Stems	E	Peru	Rojas *et al.*, 2003
Asteraceae	*Senecio culcitioides*	Aerial Parts	E	Peru	Rojas *et al.*, 2003
Asteraceae	*Pterocaulon balansae*	Aerial Parts	M	Brazil	Stopiglia *et al.*, 2011
Asteraceae	*Pterocaulon cordobense*	Aerial Parts	M	Brazil	Stopiglia *et al.*, 2011
Asteraceae	*Pterocaulon lanatum*	Aerial Parts	M	Brazil	Stopiglia *et al.*, 2011
Asteraceae	*Pterocaulon lorentzii*	Aerial Parts	M	Brazil	Stopiglia *et al.*, 2011
Asteraceae	*Pterocaulon polystachyum*	Aerial Parts	M	Brazil	Stopiglia *et al.*, 2011
Burseraceae	*Commiphora harveyi*	Leaves	Ac, Di, He, M	South Africa, Nigeria	Suleiman *et al.*, 2009
Caesalpiniaceae	*Senna alata*	Leaves	E	Guatemala	Fernández, 2005
Caesalpiniaceae	*Hymenaea courbaril*	Leaves	E	Guatemala	Sánchez, 2009
Campanulaceae	*Lobelia pyramidalis*	Aerial Parts	EO	Índia	Joshi *et al.*, 2011
Chloranthaceae	*Hedyosmum mexicanum*	Leaves	E	Guatemala	Castellanos, 2007
Clusiaseae	*Hypericum uliginosum*	Grass	E	Guatemala	Fernández, 2005
Combretaceae	*Terminalia brachystemma*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2005
Combretaceae	*Terminalia gazensis*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2005
Combretaceae	*Terminalia mollis*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2005
Combretaceae	*Terminalia prunioides*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2005
Combretaceae	*Terminalia sambesiaca*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2005

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Botanical Family	Plant Species	Plant Parts	Extract	Country	Reference
Combretaceae	*Terminalia sericea*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2005; 2010b; Masoko *et al.*, 2010a;
Combretaceae	*Combretum acutifolium*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum albopunctactum*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007; 2010b; Masoko *et al.*, 2010a
Combretaceae	*Combretum apiculatum*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum bracteosum*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum caffrum*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum celastroides* spp. *celastroides*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum celastroides* spp. *orientale*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum collinum* spp. *suluense*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum collinum* spp. *taborense*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum edwardsii*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum erythrophyllum*	Leaves	Di, He, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum hereroense*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum imberbe*	Leaves	Di	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum kraussii*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum microphyllum*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum moggii*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum molle*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum mossambicense*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum nelsonii*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007; 2010b; Masoko *et al.*, 2010a;
Combretaceae	*Combretum padoides*	Leaves	Ac, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum paniculatum*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007

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Botanical Family	Plant Species	Plant Parts	Extract	Country	Reference
Combretaceae	*Combretum petrophilum*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum woodii*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum zeyheri*	Leaves	Ac, Di, He, M	South Africa	Masoko, Picard, Eloff, 2007
Combretaceae	*Combretum vendae*	Leaves	Ac, Di, He, M	South Africa, Nigeria	Suleiman *et al.*, 2009
Compositae	*Baccharis glutinosa*	Leaves	E	Mexico	Verástegui *et al.,*1996
Cornaceae	*Curtisia dentata*	Leaves, Stems	Ac, Di, He, M	South Africa	Shai *et al.*, 2008
Euphorbiaceae	*Croton ruizianus*	Leaves, Stems	E	Peru	Rojas *et al.*, 2003
Fabaceae	*Glycyrrhiza glabra*	Root	E, EA	Índia	Fatima *et al.*, 2009
Fabaceae	*Diphysa robinioides*	Leaves	E	Guatemala	Sánchez, 2009
Geraniaceae	*Perlagonium graveolens*	-	EO	Índia	Singh *et al.*, 2012
Hydrophyllaceae	*Wigandia urens*	Leaves, Stems	E	Peru	Rojas *et al.*, 2003
Kirkiaceae	*Kirkia wilmsii*	Leaves	Ac, Di, He, M	South Africa, Nigeria	Suleiman *et al.*, 2009
Labiateae	*Satureja macrostema*	Leaves, Root	Aq, EA, MC	Mexico	Damián-Badillo *et al.*, 2008
Lamiaceae	*Origanum vulgare*	Aerial Parts	EO	Brazil	Cleff, 2008; Couto *et al*., 2015
Lamiaceae	*Salvia lavanduloides*	Leaves, Flowers	E	Guatemala	Fernández, 2005
Lamiaceae	*Rosmarinus officinalis*	Leaves	EO	Índia	Luqman *et al.*, 2007
Lamiaceae	*Ocimum basilicum*	-	EO	Índia	Sinha, Gulati, 1990
Lamiaceae	*Ocimum canum (americanum)*	-	EO	Índia	Sinha, Gulati, 1990
Lamiaceae	*Ocimum gratissimum*	-	EO	Índia	Sinha, Gulati, 1990
Lamiaceae	*Ocimum sanctum*	-	EO	Índia	Sinha, Gulati, 1990
Lauraceae	*Cinnamomum zeylanicum*	Cortex	He	Mexico	Márquez, 2010
Liliaceae	*Agapanthus africanus*	Root	E	India	Singh *et al.*, 2008
Meliaceae	*Khaya anthotheca*	Leaves	Ac, Di, He, M	South Africa, Nigeria	Suleiman *et al.*, 2009
Moraceae	*Dorstenia contrajerva*	Root	E	Guatemala	Castellanos, 2007
Myristicaceae	*Iryanthera lancifolia*	Stems	E	Peru	Rojas *et al.*, 2003
Myrtaceae	*Eucalyptus camaldulensis*	Leaves	M	Mexico	Márquez, 2010
Myrtaceae	*Eucalyptus citriodora*	-	EO	India	Akhtar *et al*., 2014
Myrtaceae	*Psidium guajava*	Leaves	Ac, He	Mexico	Márquez, 2010
Myrtaceae	*Syzygium aromaticum*	Sprouts	He	Mexico	Márquez, 2010
Myrtaceae	*Psidium acutangulum*	Leaves	E	Peru	Wen *et al.*, 2011
Ochnaceae	*Ochna natalitia*	Leaves	Ac, Di, He, M	South Africa, Nigeria	Suleiman *et al.*, 2009
Onagraceae	*Oenothera multicaulis*	Aerial Parts, Root	E	Peru	Rojas *et al.*, 2003
Piperaceae	*Piper abutiloides*	Aerial Parts	Ha	Brazil	Johann *et al.*, 2009
Poaceae	*Cymbopogon flexuosus*	-	EO	Índia	Saikia *et al.*, 2001
Poaceae	*Cymbopogon martini*	-	EO	Índia	Saikia *et al.*, 2001
Poaceae	*Cymbopogon winterianus*	-	EO	Índia	Saikia *et al.*, 2001

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Botanical Family	Plant Species	Plant Parts	Extract	Country	Reference
Polygalaceae	*Polygala campestris*	Whole Plant	Di	Brazil	Johann *et al.*, 2011
Polygalaceae	*Polygala paniculata*	Whole Plant	E	Brazil	Johann *et al.*, 2011
Polygalaceae	*Polygala sabulosa*	Whole Plant	Di, EA	Brazil	Johann *et al.*, 2011
Polygonaceae	*Rumex acetosa*	Leaves, Stems, Flowers	E	Brazil	Johann *et al.*, 2007
Rosaceae	*Rubus urticaefolius*	Leaves, Stems, Flowers	E, EA	Brazil	Johann *et al.*, 2007
Smilacaceae	*Smilax domingensis*	Leaves, Stems, Root, Flowers	E	Guatemala	Fernández, 2005
Solanaceae	*Cestrum auriculatum*	Leaves	E	Peru	Rojas *et al.*, 2003
Valerianaceae	*Valeriana prionophylla*	Root	E	Guatemala	Fernández, 2005
Verbenaceae	*Lippia graveolens*	Leaves	E, He	Guatemala	Fernández, 2005; Beteta, 2005
Zingiberaceae	*Curcuma longa*	Rhizomes	EO	Thailand	Apisariyakul, Vanittanakom, Buddhasukh, 1995
Zygophyllaceae	*Larrea tridentata*	Leaves	E	Mexico	Verástegui *et al.,*1996

Ac, acetone; Aq, aqueous; Bu, butanol; Di, dichloromethane; Ch, chloroform; CT, carbon tetrachloride; E, ethanol; EA, ethyl acetate; EO, essential oil; Ha, hydroalcoholic; He, hexane; M, methanol; MC, methanol, chloroform, - Not informed by consulted reference.

according to them, the factors that influence the outcome of antimicrobial activity of a plant are the technique applied, the strain of microorganism used, the origin of the plant and the time of its collection, the type of preparation and the amount of extract tested, among others.

Agar Diffusion

The anti-*Sporothrix* spp. activity of medicinal plants by agar diffusion test have been described and, for most authors, the studies focused on human isolates (Apisariyakul *et al.*, 1995; Saikia *et al.*, 2001; Rojas *et al.*, 2003; Damián-Badillo *et al.*, 2008; Luqman *et al.*, 2008; Verástegui *et al.*, 2008; Fatima *et al.*, 2009; Márquez, 2010; Joshi *et al.*, 2011; Wen *et al.*, 2011), according to Table II.

An Agar diffusion test consists of defying a microorganism against a biologically active substance in a solid medium culture, in which the absense of microbial growth is related to the size of the halo formed, demonstrating sensitivity of the strain to the extract (Pinto, Kaneko, Ohara, 2003). Considered one of the simplest and most trusted methods of sensitivity, this method is advantageous because of its ease of implementation and interpretation of results, as well as its use of inexpensive reagents and antibiotics without requiring special equipment. However, there is a deficiency of mechanization or automation to this method (CLSI, 2007). In regards to plant extracts, the difficulties with the test are the diffusion of the extract in the culture medium and pH of the substances used (Ostrosky *et al.*, 2008), as well as the presence of contaminants such as heavy metals, drugs and other medicinal plants (Veiga Jr., Pinto, 2005).

In this methodology, methanol-chloroformic and ethyl acetate extracts of *Satureja macrostema* (Labiateae) and *Tagetes lucida, Artemisia ludoviciana* and *Heliopsis longipes* (Asteraceae) gave growth inhibition of *S. schenckii* in the zone ranging from 1.0 to 1.99 cm (Damián-Badillo *et al.*, 2008). Better results were observed in 10% ethanolic extract of *Agave lecheguilla*, *A. picta, A. scabra* and *A. lophantha* (Agavae) between 9.0 and 16 mm at concentrations of 4.0 to 6.0 mg mL^{-1} (Verástegui *et al.*, 2008). Popularly known as licorice, ethanolic extract from the roots of *Glycyrrhiza glabra* (Fabaceae) also inhibited the growth of *S. schenckii* at 5 mm diameter, as well as the active constituent of this plant – glabridin – and the ethyl acetate fraction of root with 6 and 7 mm, respectively (Fatima *et al.*, 2009).

In traditional Peruvian medicine, a study with 36 ethanolic extracts of 24 plants from Asteraceae family showed the inhibition of *S. schenckii* to *Croton ruizianus, Iryanthera lancifolia, Oenothera multicaulis, Ophryosporus peruvianus, Senecio culcitioides* and

TABLE II - Results of agar diffusion test done in plants with antifungal activity against *Sporothrix schenckii* complex and its characteristics of solvent extract tested, botanical family, plant species and fungal strain origin according to reference that demonstrated values of inhibition zone

Botanical Family	Plant Species	Solvent Extract	Origin of *Sporothrix* spp.	Inhibition Zone*	Reference
Agavaceae	*Agave lecheguilla*	Ethanol	Human	10 mm	Verastegui *et al*., 2008
Agavaceae	*Agave lophantha*	Ethanol	Human	10 mm	Verastegui *et al.*, 2008
Agavaceae	*Agave picta*	Ethanol	Human	16 mm	Verastegui *et al.*, 2008
Agavaceae	*Agave scabra*	Ethanol	Human	9 mm	Verastegui *et al.*, 2008
Asteraceae	*Artemisia ludoviciana*	Ethanol	Unspecified	1to 1.99 cm	Damián-Badillo *et al.*, 2008
Asteraceae	*Artemisia ludoviciana*	Methanol	Unspecified	1 to 1.99 cm	Damián-Badillo *et al.*, 2008
Asteraceae	*Heliopsis longipes*	Ethanol	Unspecified	1 to 1.99 cm	Damián-Badillo *et al.*, 2008
Asteraceae	*Ophryosporus peruvianus*	Ethanol	Human	13 mm	Rojas *et al.*, 2003
Asteraceae	*Senecio culcitioides*	Ethanol	Human	15 mm	Rojas *et al.*, 2003
Asteraceae	*Tagetes lucida*	Methanol	Unspecified	1 to 1.99 cm	Damián-Badillo *et al.*, 2008
Asteraceae	*Tagetes lucida*	Ethanol	Unspecified	1 to 1.99 cm	Damián-Badillo *et al.*, 2008
Campanulaceae	*Lobelia pyramidalis*	Essential oil	MTCC† 1359	13 mm	Joshi *et al.*, 2011
Euphorbiaceae	*Croton ruizianus*	Ethanol	Human	13 mm	Rojas *et al.*, 2003
Fabaceae	*Glycyrrhiza glabra*	Ethanol	AIIMS◊	5 mm	Fatima *et al.*, 2009
Fabaceae	*Glycyrrhiza glabra*	Acetyl acetate	AIIMS◊	7 mm	Fatima *et al.*, 2009
Hydrophyllaceae	*Wigandia urens*	Ethanol	Human	13 mm	Rojas *et al.*, 2003
Labiateae	*Satureja macrostema*	Ethanol	Unspecified	1 to 1.99 cm	Damián-Badillo *et al.*, 2008
Labiateae	*Satureja macrostema*	Methanol	Unspecified	1 to 1.99 cm	Damián-Badillo *et al.*, 2008
Lamiaceae	*Rosmarinus officinalis*	Essential oil	AIIMS◊	< 5 mm	Luqman *et al.*, 2007
Lauraceae	*Cinnamomum zeylanicum*	Hexane	Unspecified	14 mm	Márquez, 2010
Myristicaceae	*Iryanthera lancifolia*	Ethanol	Human	13 mm	Rojas *et al.*, 2003
Myrtaceae	*Eucalyptus camaldulensis*	Acetone	Unspecified	12 mm	Márquez, 2010
Myrtaceae	*Eucalyptus citriodora*	Essential oil	MTCC† 1359	6.67 to 27 mm	Akhtar *et al.*, 2014
Myrtaceae	*Psidium acutangulum*	Ethanol	IHEM§15503	22 mm	Wen *et al.*, 2011
Myrtaceae	*Psidium guajava*	Methanol	Unspecified	16 mm	Márquez, 2010
Myrtaceae	*Syzygium aromaticum*	Hexane	Unspecified	43 mm	Márquez, 2010
Onagraceae	*Oenothera multicaulis*	Ethanol	Human	15 to 19 mm	Rojas *et al.*, 2003
Poaceae	*Cymbopogon flexuosus*	Essential oil	Human	35 mm	Saikia *et al.*, 2001
Poaceae	*Cymbopogon martini*	Essential oil	Human	19 mm	Saikia *et al.*, 2001
Poaceae	*Cymbopogon winterianus*	Essential oil	Human	12 mm	Saikia *et al.*, 2001
Solanaceae	*Cestrum auriculatum*	Ethanol	Human	25 mm	Rojas *et al.*, 2003
Zingiberaceae	*Curcuma longa*	Essential oil	Human	3 mm	Apisariyakul, 1995

*The resuls were described according authors reference and only species plants with results of inhibition zone were considered; †Microbial Type Culture Collection and Gene Bank (Chandigarh, India); ◊All India Institute of Medical Sciences (New Delhi, India); §Instutute of Hygiene and Epidemiology-Mycology Laboratory (Brussels, Belgium).

Wigandia urens that promoted halo of growth inhibition of 13 to 19 mm and the best anti-*Sporothrix* spp. activity was related to *Cestrum auriculatum* with halo of 25 mm, including against strains with no susceptibility to amphotericin B and fluconazole, indicating the importance of the search for new compounds for resistant isolates (Rojas *et al.*, 2003).

In another similar study, ethanolic extracts of *Calycophyllum spruceanum* (Rubiaceae), *Spondia mombin* (Anacardiaceae) and *Thevetia peruviana* (Apocynaceae) did not show anti-*Sporothrix* spp. activity, but leaves of *Psidium acutangulum* (Myrtaceae) inhibited *S. schenckii* with an halo of 22 mm and the active chemical composition "3'-formil-2',4',6'-trihidroxidihidrochalcone" was individually tested against strains resistants to amphotericin B and fluconazole by broth microdilution technique and showed MIC of 32 µg ml^{-1}, being considered promising for therapeutic alternatives in sporotrichosis (Wen *et al.*, 2011).

Popularly known as clove, extracts of hexane and acetone at 20% of *Syzygium aromaticum* (Myrtaceae) had greater anti-*Sporothrix* spp. activity with inhibition growth of 28 mm to 43 mm in the disc diffusion method on agar and the extracts of *Cinnamomum zeylanicum* (Lauraceae), *Eucalyptus camaldulensis* and *Psidium guajava* (Myrtaceae), popularly known as cinnamom, eucalyptus and guava, respectively, that inhibited *S. schenkii* in zones of 10 to 23 mm, but the most of the methanolic extracts of these tested plants did not show antifungal activity (Márquez, 2010). Still in Myrtaceae family, the ointment formulation of *Eucalyptus citriodora* Hook at 2% was more pronounced against *S. schenckii* with zone of growth inhibition of 27 mm, but cream formulation with essential oil and the proper essential oil of this plant had also fungistatic activity between 6.67 to 19.67 mm through agar disc diffusion (Akhtar *et al.*, 2014).

In another study, *Cymbogon winterianus* (Poaceae) essential oil constituted a potential antifungal product (Pereira *et al.*, 2011). *S. schenckii* was inhibited in the growth zone of 12 mm at dilution of 1/800 for *C. winterianus*, known as citronella, while *C. martini* and *C. flexuosus* inhibited with 19 mm and 35 mm, respectively, at dilution of 1/1600 (Saikia *et al*., 2001). In the *Ocimum* genus (Lamiaceae), the essential oils of *O. sanctum, O. canum (O. americanum)* and *O. gratissimum* was conferred activity between 8 and 14 mm of diameter (Sinha, Gulati, 1990). In other botanical species, *S. schenckii* has been inhibited by *Lobelia pyramidalis* (Campanulaceae), known as lobelia, with 13 mm of diameter (Joshi *et al.*, 2011); *Curcuma longa* (Zingiberaceae), known as turmeric, with 3 mm (Apisariyakul *et al.*, 1995), and *Rosmarinus officinalis* (Lamiaceae), known as rosemary, with 2.5 mm (Luqman *et al.*, 2007). In commercially-available natural products from *Perlagonium graveolens* (Geraniaceae), Singh *et al.* (2012) showed that the compounds of terpineol and geranium oil had antifungal activity, while geraniol, phenyl ethyl alcohol and citronella acetate had not shown satisfactory activity.

In the methodology adapted by Brancato and Golding (1953), Beteta (2005) tested aqueous extracts and portions extracted with hexane, chloroform and ethyl acetate derived from the leaves of *Lippia graveolens* (Verbenaceae) and the flowers of *Bourreria huanita* (Boraginaceae) and showed that the antifungal activity was conferred only to *L. graveolens* whose hexanic fraction inhibited the yeast and filamentous phases when tested at a concentration of 0.5 mg mL^{-1}, while the ethanolic fraction inhibited only the filamentous phase at 0.25 mg ml^{-1}.

Ethanolic extracts of seeds of *Phasoelus lunatus* (Fabaceae) and leaves of *Cassia grandis* (Fabaceae), *Diphysa robinioides* (Fabaceae), *Hymenaea courbaril* (Caesalpiniaceae), *Phasoelus vulgaris* (Fabaceae), *Senna occidentalis* (Fabaceae) and *Vicia faba* (Fabaceae) were already tested and proved no activity against the yeast phase, but the filamentous phase showed sensitivity only to extracts of *H. courbaril* and *D. robinioides* tested at the concentration of 1 mg mL^{-1} and the MIC value of 0.5 mg mL^{-1} and 1 mg mL^{-1}, respectively (Sánchez, 2009).

In another study, yeast and filamentous phases of *S. schenckii* were inhibited by the ethanolic extracts from roots of *Dorstenia contrajerva* (Moraceae) and leaves of *Hedyosmum mexicanum* (Chloranthaceae), being the mycelial phase inhibited at MIC of 0.1 mg mL^{-1} and 0.05 mg mL^{-1}, respectively, but the yeast phase was only inhibited by *H. mexicanum* at MIC of 0.1 mg mL^{-1}, however, the extracts from leaves of *Baccharis triversis* (Asteraceae), *Lippia chiapasensis* (Verbenaceae) and *Ocimum micranthum* (Lamiaceae) and the roots of *Petiveria alliaceae* (Phytolaccaceae) did not have activity against *S. schenckii* at maximum concentration of 0.2 mg mL^{-1} for both fungal phases (Castellanos, 2007). According to these authors, the plants that did not show satisfactory activity may have active chemical compounds in other botanical portions or when tested in higher concentrations, which does not rule out the possibility of possessing potential antifungal activity.

In ethanolic extracts from twelve plants native to Guatemala at the concentration of 1 mg mL^{-1} using agar diffusion adapted by Brancato and Golding (1953), the extracts of *Hypericum uliginosum* (Clusiaseae), *Smilax*

domingensis (Smilacaceae)*, Salvia lavanduloides* (Lamiaceae) and *Senna alata* (Caesalpiniaceae) inhibited *S. schenckii* in the yeast phase, while only the extracts of *Lippia graveolens* (Verbenaceae) and *Valeriana prionophylla* (Valerianaceae) showed activity for both phases of this dimorphic fungus. The other tested plants – *Cornutia pyramidata* (Verbenaceae), *Quercus crispifolia* (Fagaceae)*, Solanum americanum* (Solanaceae*)*, *Sterculia apetala* (Malvaceae), *Tabebuia rosea* (Bignoniaceae) and *Tithonia diversifolia* (Asteraceae) – did not exhibit activity against *S. schenckii* (Fernández, 2005).

According to Fernández (2005), the yeast phase would be more susceptible to the extracts for the lesser amount of ergosterol present in the membrane cell at this phase, leading to a greater susceptibility to permeability changes, as well as by the biosynthesis of ergosterol inhibition and other steroids by the active compounds present in the extracts. Another hypothesis of the antifungal mechanism would be the inhibition of its triglycerides and phospholipids biosynthesis or the inhibition of oxidative and peroxidative enzymatic activity that results in accumulation of toxic concentrations of hydrogen peroxide and leads to deterioration of subcellular organs and cell necrosis.

Broth Microdilution Method

Plants from different botanical families presented anti-*Sporothrix* spp. activity through tests of broth microdilution in standard strains isolated from humans and felines (Verástegui *et al.*, 1996; Johann *et al.*, 2007; Luqman *et al.*, 2007; Cleff *et al.*, 2008; Fatima *et al.*, 2009; Johann *et al.*, 2011; Joshi *et al.*, 2011; Stopiglia *et al.*, 2011). This method is based on the proportion of microbial growth in liquid medium challenged with the concentration of the measured substance using a 96-well microplate (CLSI, 2002; Pinto *et al.*, 2003). Among the main advantages cited of this quantitative test are savings in space and reagents, generation of quantitative results through values of minimum inhibitory concentration and the use of pre-fabricated microdilution plates (CLSI, 2002). However, the cost of microdilution plates is a disadvantage, because the realization of a large number of antifungal tests may elevate costs (CLSI, 2002). Furthermore, Eloff (1998) observed compounds precipitation in some plants extracts and interference in the analysis by the high concentration of chlorophyll. In spite of these factors, this method is still considered advantageous for its high sensitivity and reproducibility in relation to other techniques (Eloff, 1998). The results of plants with anti-*Sporothrix* spp. activity confirmed by broth microdilution technique, as well as their botanical information are displayed in Table III.

Lamiaceae family is known with potential antifungal for controlling the growth of pathogenic fungi and the occurrence of mycosis (Souza *et al*., 2010). Rosemary oil (*Rosmarinus officinalis*) showed *in vitro* activity against *S. schenckii* at concentration of 11 mg mL^{-1} (Luqman *et al.*, 2007), as well oregano oil (*Origanum vulgare*), that inhibited *S. schenckii* concentrations between 250 to 500 µL mL^{-1} (Cleff *et al.*, 2008; 2010). In *S. schenckii* and *S. brasiliensis,* Couto *et al*. (2015) showed the antifungal potential of oregano oil, as well as in its major compound (γ-terpinene), which caused morphological alterations in hyphae and reduced the adhered conidia numbers.

From the plants used in traditional medicine in Brazil, Johann *et al.* (2011) exhibited that ethanolic and ethyl acetate extracts of *Rubus urticaefolius* (Rosaceae) inhibited the fungal growth at the concentration of 125 µg mL^{-1}, while *Rumex acetosa* (Polygonaceae) demonstrated activity at 1000 µg mL^{-1}. The same activity was observed in the essential oil of *Lobelia pyramidalis* (Campanulaceae), which inhibited the fungal growth at MIC of 6.25 mg mL^{-1} (Joshi *et al.*, 2011). Fatima *et al*. (2009) showed greater activity of ethanolic and hexanic extracts of *Schinus terebinthifolius* (Anacardiaceae) at 15 µg ml^{-1}, as well as the ethanolic extracts at 15% from roots of *Glycyrriza glabra* (Fabaceae) at 1 mg mL^{-1} and glabridin and ethyl acetate fraction at 0.25 µg mL^{-1}. Other plants were tested on *S. schenckii*, such as *Piper regnelii* (Piperaceae), *Herissantia crispa* (Malvaceae), *Baccharis dracunculifolia* (Asteraceae), *Inga dulcis* (Leguminosae) and *Alternanthera brasiliana* (Amaranthaceae) and did not show antifungal activity (Johann *et al.*, 2007). In the Chihuahuan region (encompassing parts of Northern Mexico and the Southwestern United States), fungistatic activity was observed in the ethanolic extract at 80% of the leaves from *Baccharis glutinosa* (Compositae) and *Larrea tridentata* (Zygophyllaceae) and roots of *Agave lecheguilla* (Agavaceae) at MIC of 12, 16 and 5 mg mL^{-1}, respectively (Verástegui *et al.*, 1996).

In the Piperaceae family, *Piper abutiloides* presented MIC value of 125 µg mL^{-1} when tested in form of hydroalcoholic extract at 80%, but hexane, dichloromethane, ethyl acetate and aqueous extractions did not show antifungal activity at the maximum tested concentration of 1000 µg mL^{-1} (Johann *et al.*, 2009). In the extract with antifungal activity, these authors isolated the compounds pseudodillapiol, eupomatenoid-6 and conocarpan, which provided fungistatic activity at MIC of 12.5 µg $spot^{-1}$, 25 µg $spot^{-1}$ and 50 µg $spot^{-1}$ respectivelly, when individually tested against *S. schenckii*.

TABLE III - Results of microdilution test of plants species with activy against strains of *Sporothrix schenckii* complex and their different values of minimal inhibitory concentration according to references and solvent extract with action

Botanical Family	Plant Species	Solvent Extract	Origin of *Sporothrix* spp.	Minimal Inhibitory Concentration	Reference
Agavaceae	*Agave lecheguilla*	Ethanol	Human	5.0 mg mL^{-1}	Verástegui *et al.,*1996
Anacardiaceae	*Schinus terebinthifolius*	Ethanol, Hexane	ATCC♦ 22019	15 µg mL^{-1}	Johann *et al*., 2007
Asteraceae	*Pterocaulon balansae*	Methanol	Human	625 µg mL^{-1}	Stopiglia *et al.*, 2011
Asteraceae	*Pterocaulon cordobense*	Methanol	Human	625 µg mL^{-1}	Stopiglia *et al.*, 2011
Asteraceae	*Pterocaulon lanatum*	Methanol	Human	625 µg mL^{-1}	Stopiglia *et al.*, 2011
Asteraceae	*Pterocaulon lorentzii*	Methanol	Human	625 µg mL^{-1}	Stopiglia *et al.*, 2011
Asteraceae	*Pterocaulon polystachyum*	Methanol	Human	156 µg mL^{-1}	Stopiglia *et al.*, 2011
Campanulaceae	*Lobelia pyramidalis*	Essential oil	MTCC† 1359	6.25 mg mL^{-1}	Joshi *et al.*, 2011
Compositae	*Baccharis glutinosa*	Ethanol	Human	12 mg mL^{-1}	Verástegui *et al.,*1996
Fabaceae	*Glycyrrhiza glabra*	Ethanol	AIIMS◊	1 mg mL^{-1}	Fatima *et al.*, 2009
Lamiaceae	*Origanum vulgare*	Essential oil	Human; Feline	250 µL mL^{-1}	Cleff *et al*., 2008
Lamiaceae	*Origanum vulgare*	Essential oil	Human; ATCC 1099-18; ATCC 5110; IPEC* 15383; IPEC 17943	216 to 1735 µg mL^{-1}	Couto *et al*., 2015
Lamiaceae	*Rosmarinus officinalis*	Essential oil	AIIMS◊	11 mg mL^{-1}	Luqman *et al.*, 2007
Piperaceae	*Piper abutiloides*	Hydroalcoholic	ATCC♦ 20679	125 µg mL^{-1}	Johann *et al.*, 2009
Polygalaceae	*Polygala campestris*	Dichloromethane	ATCC♦ 20679	500 µg mL^{-1}	Johann *et al.*, 2011
Polygalaceae	*Polygala paniculata*	Ethanol	ATCC♦ 20679	1000 µg mL^{-1}	Johann *et al.*, 2011
Polygalaceae	*Polygala sabulosa*	Acetyl acetate	ATCC♦ 20679	30 µg mL^{-1}	Johann *et al.*, 2011
Polygonaceae	*Rumex acetosa*	Ethanol	ATCC♦ 22019	1000 µg mL^{-1}	Johann *et al.*, 2007
Rosaceae	*Rubus urticaefolius*	Acetyl acetate, Ethanol	ATCC♦ 22019	125 µg mL^{-1}	Johann *et al.*, 2007
Zygophyllaceae	*Larrea tridentata*	Ethanol	Human	16 mg mL^{-1}	Verástegui *et al.,*1996

♦American Type Culture Collection (Manassas, VA, USA); †Microbial Type Culture Collection and Gene Bank (Chandigarh, India); *Instituto de Pesquisa Clínica Evandro Chagas (Rio de Janeiro, Brazil); ◊All India Institute of Medical Sciences (New Delhi, India).

In the *Polygala* genus (Polygalaceae family), the ethyl acetate and dichloromethane of *P. sabulosa* had the better activity at MIC of 30 µg mL^{-1} and 250 µg mL^{-1}, respectively, and dichloromethanic and ethanolic extracts of *P. campestris, P. sabulosa* and *P. paniculata* has activity between 500 to 1000 µg mL^{-1}, but no activity was observed in extracts from *P. cyparissias.* The authors isolated the compounds "prenyloxycoumarin" and "1,2,3,4,5,6-hexanehexol" from *P. sabulosa* and these showed activity in the MIC value of 125 µg mL^{-1} and 250 µg mL^{-1}, respectively (Johann *et al.*, 2011).

Stopiglia *et al.* (2011) demonstrated *in vitro* efficacy of plants from the *Pterocaulon* genus (Asteraceae family) against 24 strains of *S. schenckii*, and the methanolic extract at 10% of *P. polystachyum, P. lorentzii, P. lanatum, P. cordobense* and *P. balansae* had inhibitory and fungicidal activity. Of these, the extract of *P. polystachyum* showed greater results with MIC ranged of 156 to 312 µg mL^{-1} and

MFC varied between 312 to 1250 μg mL^{-1}.

A variation of the broth microdilution technique, the Serial Microdilution Method is performed through the confirmation of the MIC value by the use of *p*-iodonitrotetrazolium violet (INT) in each well-test as a fungal growth indicator, indicated by reduction of the red color of INT formazan and evaluated within a period of 24 to 48 hours of incubation (Eloff, 1998; Masoko, Picard, Eloff, 2005). According to Table IV, acetonic, hexanic, dichloromethanic and methanolic extracts from leaves of six native species of trees in South Africa, belonging to the genus *Terminalia* (Combretaceae family) showed high activity in the MIC values of 0.02 to 0.64 mg mL^{-1} (Masoko, Picard, Eloff, 2005), as well as extracts from 24 plants of *Combretum* genus (Combretaceae) (Masoko, Picard, Eloff, 2007).

Suleiman *et al.* (2009) showed the anti-*Sporothrix* spp. activity of different extracts from leaves of native species trees of South Africa: *Combretum vendae* (Combretaceae), *Commiphora harveyi* (Burseraceae), *Khaya anthotheca* (Meliaceae), *Kirkia wilmsii* (Kirkiaceae), *Loxostylis alata* (Anacardiaceae), *Ochna natalitia* (Ochnaceae) and *Protorhus longifolia* (Anacardiaceae). In different extracts at 10% of *L. alata,* acetonic extract of *L. alata* exhibited better antifungal activity in MIC of 0.04 mg mL^{-1} in 24 hours and 0.08 mg mL^{-1} in 48 hours (Suleiman *et al.*, 2009) and other fractions of the *L. alata* had synergistic activity against *Sporothrix* spp. in the MIC of 0.2 to 1.88 mg mL^{-1} (Suleiman *et al.*, 2012). These activities can be explained by the lupeol compound, which showed anti-*Sporothrix* spp. activity when individually tested at the MIC values of 57 μg mL^{-1} (Suleiman *et al.*, 2013). Lupeol isolated from leaves and stem barks of *Curtisia dentata* B. (Cornaceae) showed higher activity (12 μg mL^{-1}) when compared with betulinic acid, ursolic acid and 2-α-hydroxy ursolic acid isolated, that had also activity between 16 to 32 μg mL^{-1} (Shai *et al.*, 2008).

In another study, the ethanolic extract of the rhizomes of *Agapanthus africanus* L. (Liliaceae) had activity against *Sporothrix* spp. with MIC value of 250 μg mL^{-1}, and the compound saponin was isolated from this extract and was responsible for antifungal activity in MIC of 15.6 μg mL^{-1} (Singh *et al.*, 2008).

Bioautographic Assay

Many researchers carry out bioautographic assay to detect new or unidentified compounds in plants of interest, in order to pursue and deepen the studies in cases of confirmed antimicrobial action (Betina, 1973). This test is based on assessing the inhibition zone afforded by the extract of interest, through the addition of this extract in silica gel plates and further immersion in a fungal suspension and addition of *p*-iodonitrotetrazolium violet (Rahalison *et al.*, 1993). Among eight plants popularly used in traditional Brazilian medicine, Johann *et al.* (2007) measured the MIC values by broth microdilution technique only of six plants of different extracts, because those were effective against a several number of pathogens tested by bioautographic assay and the ethanolic extract of leaves from *S. terebinthifolius* (Anacardiaceae) showed better activity against *S. schenckii* at 15 μg mL^{-1}.

In plants from *Polygala* genus, five species presented activity in the bioautographic assay and were submitted to broth microdilution test, demonstrating that ethanolic extract of *P. paniculata* (1000 μg mL^{-1}) and the fractions of dichloromethane and ethyl acetate of *P. sabulosa* (250 μg $mL^{-1}$and 30 μg mL^{-1}, respectively) showed good antifungal activity against *S. schenckii* (Johann *et al.*, 2011).

Agar Cup Method

Brazilian propolis produced by bees that collected pollen from *Baccharis dracunculifolia* (Asteraceae) and araucaria (*Araucaria* spp. – Araucariaceae) showed antifungal activity in the 30% ethanolic extract at the concentration of 16 to 2.0 mg mL^{-1} by the agar cup method, in which the antifungal activity is measured by inhibition zone diameter. The inhibitory action of both plants occurred when tested individually and jointly against *S. schenckii,* whose inhibition diameter ranged between 16 to 24 mm and the lowest concentration tested (2 mg mL^{-1}) of *B. dracunculifolia* was able to inhibit the fungal growth up to 19 mm diameter (Salomão *et al.*, 2008).

The small annual herb *Cuminim cyminum* L. (Apiaceae), popularly known as cumin, is the second most popular spice in the world, after black pepper, and showed activity against *S. schenckii* in the zone of inhibition of 18 mm to essential oil, 12 mm to methanol extract and 0.3 mm to hydroalcoholic extract, but aqueous extract of this plant did not show anti-*Sporothrix* spp. activity when the products where tested at concentration of 0.5 mg mL^{-1} (Chaudhary, Husain, Ali, 2014).

IN VIVO STUDIES

In vivo studies with aqueous creams containing 20% of acetone extracts (2 g of extract in 10 g of cream) from the leaves of different species of Combretaceae were evaluated in experimental cutaneous sporotrichosis and showed wound-healing properties when administered topically three times per week in rats *Wistar*. The preparations

TABLE IV - Results of Minimal Inhibitory Concentration (MIC) in the serial microdilution dilution method in different extracts of medicinal plants with activity against *Sporothrix* spp. in the period of 24 hours

Botanical Family	Plant Species	Solvent Extract	Origin of *Sporothrix* spp.	MIC at 24 hours*	Reference
Anacardiaceae	*Loxostylis alata*	Acetone	Unspecified	0.04 mg mL^{-1}	Suleiman *et al.*, 2009
		Methanol, Butano, Hexane, Chloroform, Carbon Tetrachloride, Water	Unspecified	0.2 to 1.88 mg mL^{-1}	Suleiman *et al.*, 2012
	Protorhus longifolia	Dichloromethane	Unspecified	0.84 mg mL^{-1}	Suleiman *et al.*, 2009
Burseraceae	*Commiphora harveyi*	Acetone	Unspecified	0.31 mg mL^{-1}	Suleiman *et al.*, 2009
Combretaceae	*Combretum acutifolium; C. albopunctactum; C. apiculatum; C. edwardsii; C. hereroense; C. moggi; C. nelsonii; C. zeyheri*	Acetone	Equine	0.02 to 0.04 mg mL^{-1}	Masoko, Picard, Eloff, 2007
	C. apiculatum; C. edwardsii; C. moggi; C. molle; C. mossambicense; C. petrophilum	Methanol	Equine	0.02 to 0.08 mg mL^{-1}	Masoko, Picard, Eloff, 2007
	C. apiculatum; C. microphyllum; C. mossambicense; C. paniculatum	Dichloromethane	Equine	0.02 to 0.04 mg mL^{-1}	Masoko, Picard, Eloff, 2007
	C. bracteosum; C. hereroense; C. mossambicense	Hexane	Equine	0.02 to 0.04 mg mL^{-1}	Masoko, Picard, Eloff, 2007
	C. celastroides spp. *orientale; C. collinum* spp. *suluense; C. woodii*	Acetone	Equine	0.08 mg mL^{-1}	Masoko, Picard, Eloff, 2007
	C. caffrum	Methanol	Equine	0.32 mg mL^{-1}	Masoko, Picard, Eloff, 2007
	C. celastroides spp. *celastroides*	Methanol	Equine	0.16 mg mL^{-1}	Masoko, Picard, Eloff, 2007
	C. collinum spp. taborense; C. kraussii	Hexane, Dichloromethane	Equine	0.16 mg mL^{-1}	Masoko, Picard, Eloff, 2007
	Combretum erythrophyllum	Hexane	Equine	0.32 mg mL^{-1}	Masoko, Picard, Eloff, 2007
	Combretum imberbe	Dichloromethane	Equine	0.32 mg mL^{-1}	Masoko, Picard, Eloff, 2007
	Combretum padoides	Acetone	Equine	0.32 mg mL^{-1}	Masoko, Picard, Eloff, 2007
	Combretum vendae	Hexane	Unspecified	0.13 mg mL^{-1}	Suleiman *et al.*, 2009
	Terminalia brachystemma; T. mollis	Dichloromethane	Equine	0.02 mg mL^{-1}	Masoko, Picard, Eloff, 2005
	Terminalia gazensis; T. prunioides; T. sambesiaca	Acetone	Equine	0.02 to 0.08 mg mL^{-1}	Masoko, Picard, Eloff, 2005
	Terminalia prunioides	Hexane	Equine	0.04 mg mL^{-1}	Masoko, Picard, Eloff, 2005

TABLE IV - Results of Minimal Inhibitory Concentration (MIC) in the serial microdilution dilution method in different extracts of medicinal plants with activity against *Sporothrix* spp. in the period of 24 hours (cont.)

Botanical Family	Plant Species	Solvent Extract	Origin of *Sporothrix* spp.	MIC at 24 hours*	Reference
Combretaceae	*Terminalia sericea*	Methanol	Equine	0.02 mg mL^{-1}	Masoko, Picard, Eloff, 2005
Kirkiaceae	*Kirkia wilmsii*	Acetone	Unspecified	0.26 mg mL^{-1}	Suleiman *et al.*, 2009
Meliaceae	*Khaya anthotheca*	Acetone	Unspecified	0.11 mg mL^{-1}	Suleiman *et al.*, 2009
Ochnaceae	*Ochna natalitia*	Hexane	Unspecified	0.08 mg mL^{-1}	Suleiman *et al.*, 2009

* The extrats types of considered plants were those with minimum values of inhibitory concentration at 24 hours.

of leaves from *Combretum imberbe, C. nelsonii, C. albopunctatum* and *Terminalia sericea* (Combretaceae) have produced reversal of lesions in 15 days, confirming *in vivo* antifungal activity. Irritating and damaging effects from the same plants on skin wounds were not observed, indicating the absence of adverse effects on healthy skin of the tested animals (Masoko *et al.*, 2010a; Masoko, Picard, Eloff, 2010b).

The promising use of medicinal plants in sporotrichosis encourages scientific researchers to find a new antifungal product. However, there are few studies proving the anti-*Sporothrix* spp. activity of medicinal plants. More studies about safe concentrations of their use must be performed because these plants can present chemical elements with capacity to cause toxic effects (Veiga Jr., Pinto, 2005; Leal *et al.*, 2013). More studies are needed to determine medicinal plants´ safe use with little or no adverse effects in the patient.

CONCLUSION

In vitro studies suggest plants as sources of new promising molecules in the control and treatment of sporotrichosis, especially species belonging to the families Combretaceae, Asteraceae and Lamiaceae. Due to various protocols and methodologies used in the studies, as well as to the different tested concentrations, we emphasize the difficulty in comparing the fungistatic and fungicidal results of plant extracts and it is not possible to attribute the plants with better activity. Furthermore, the lack of *in vivo* studies of plants was noticed, which reveals the need for deeper studies focussed on the action mechanism of the plants, as well as their toxicity, side effects and possibility of drug interactions in order to understand the safe use of medicinal plants for the treatment of sporotrichosis.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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