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REVIEW ARTICLE

BRAZILIAN PEPPER TREE: REVIEW OF PHARMACOLOGY

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Summary

Brazilian pepper tree (*Schinus terebinthifolius* Raddi) from the *Anacardiaceae* family is native to Central and South America. In folk medicine, *S. terebinthifolius* has been used as a remedy for ulcers, respiratory problems, wounds, rheumatism, gout, diarrhea, skin ailments and arthritis, as well as to treat tumors and leprosy. The Brazilian pepper tree has various biological properties and it is a source of many bioactive compounds. Several classes of compounds can be found in extracts obtained from these plants, such as terpenes and flavonoids. Essential oils obtained by steam distillation or extraction by solvents from berries or leafs is rich in monoterpenes and shows interesting antioxidant activity. It has displayed good-to-very strong in vitro antifungal actions against numerous fungi, as well as Candida. The essential oil and leaves have demonstrated in vitro antibacterial activity against numerous bacterial strains.

Key words: Brazilian pepper tree; Schinus terebinthifolius; ethnobotanics; traditional medicine; pharmacology; toxicology

INTRODUCTION

Medicinal plants have been part of our society in preventing diseases since the dawn of civilization, and developing countries have used these plants for centuries as an alternative treatment for health problems. Brazil has the largest diversified forest reserve on the planet. Many species are used for medicinal purposes with low or no evidence of its properties. The interest in discovering new substances stimulated scientists from different areas to look for flora with medicinal properties normally used by the population. Such a plant is also Brazilian pepper tree (*Schinus terebinthifolius* Raddi) from the *Anacardiaceae* family native to Central and South America. In Brazil this tree that can reach 10 m height and 1–3 m in diameter and is known as "aroeira-vermelha" or "aroeira-pimenteira" (Morton, 1978; Lorenzi, 1992). The genus *Schinus* is indigenous to Argentina, Brazil, Paraguay, Uruguay, Chile, Bolivia, and Peru (Barkley, 1944). The plant has been spread around the world as an ornamental beginning in the mid to late 1800s (Mack, 1991). Naturalization of Brazilian pepper tree has occurred in over 20 countries worldwide throughout subtropical regions (Ewel et al., 1982). Brazilian pepper-tree is one of the most aggressive of these non-native invaders. Where once there were ecologically productive mangrove communities, now there are pure stands of Brazilian pepper-trees (Lamarque et al., 2011).

The Brazilian pepper tree has various biological properties such as insecticidal activity and it is a source of many bioactive compounds (Silva et al., 2010). Its leaves are popularly used in remedies for healing ulcers and wounds,

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combating oral candidiasis in children, and for producing infusions considered to have anti-rheumatic properties (Lindenmaier, 2008). Some of the compounds from Brazilian pepper tree leaves with proven biological activities are terpenes that induce apoptosis and protect against metastasis (Matsuo et al., 2011), hydroalcoholic extract had a favorable effect in the healing process (Branco Neto et al., 2006; Lucena et al., 2006), essential oil obtained by steam distillation from berries of pepper tree inhibits mitosis in plant cells (Pawlowski et al., 2012) and have anticancer activities against some human cancer cells (Bendaoud et al., 2010), ethyl acetate fraction of leaves has anti-allergic activity (Cavalher-Machado et al., 2008), polyphenols isolated from plant induce apoptotic and autophagic cell death of cells (Queires et al., 2006), aromatic compounds have ability to treat allergies (Pawlowski et al. 2012), and a specific leaf lectin exhibits antimicrobial properties (Gomes et al., 2013). Larvicidal activity against *A. aegypti* has been detected in a dichloromethane extract from *S. terebinthifolius* leaves and an essential oil extracted from its fruit (Silva et al., 2010).

BOTANICS AND ETHNOBOTANICS

Brazilian pepper tree (*Schinus terebinthifolius* Raddi), also known as Felfel Aareed, is a shrub or small tree up to 10 m tall, native of Argentina, Paraguay, and Brazil (Fig. 1). The leaves have reddish colour and have 3 to 13 sessile, oblong or elliptic, finely toothed leaflets, 2.5 to 5 cm long. Leaves smell of turpentine when crushed. The plants have separate male or female flowers and each sex occurs in clusters on separate plants. The male and female flowers are both white and are made up of five parts with male flowers having 10 stamens in 2 rows of 5. Petals are 1.5 mm long. The male flowers also have a lobed disc within the stamens. Flowering occurs predominantly from September through November. Male flowers last only 1 day. Female flowers last up to 6 days and are pollinated by insects. The fruits are in clusters, glossy, green and juicy at first, becoming bright red on ripening, and 6 mm wide. Fruits usually mature by December. The red skin dries to become a papery shell surrounding the seed. The seed is dark brown and 0.3 mm in diameter (Morton et al., 1978).

Figure 1. Brazilian pepper trees Schinus terebinthifolius Raddi (Aroeira-da-praia) and a detail view of the fruits (inset).

Brazilian pepper tree is known under local name „Aroeira“ whose stem bark is used to treat inflammations, scabies, sore throat and itching (Gazzaneo et al., 2005; Castro et al., 2011) and this tree is of interest of ethnobotanical studies of the Brazilian program on medicinal germplasm conservation, collection and characterization and *in situ* conservation (Veira, 1999). The importance of medicinal plants can be attributed to accessibility, as well as the confidence in phytotherapy, according to the witnessed positive effects from their use.

ENVIRONMENT

Invasive species are a management concern on protected areas worldwide and Brazilian pepper-tree is one of the most aggressive of these non-native invaders. Where once there were ecologically productive mangrove communities, now there are pure stands of Brazilian pepper-trees (Donelly et al., 2008). Scrub and pine flatwood communities are also being affected by this invasion (Manrique et al., 2013). The Brazilian pepper tree was introduced to the United States in the 1800s and has since become a category one invasive plant in Florida. It has aggressively spread to about 3000 km^2 of terrestrial surface (Dawkins and Esiobu, 1016). Nearly all terrestrial ecosystems in central and southern Florida are being encroached upon by the Brazilian pepper tree (Ewel, 1986).

Jungles of pepper tree have also crowded out native vegetation over vast areas of the Bahamas, as in all the islands of Hawaii (Degener, 1946). When in bloom, the tree is a major source of respiratory difficulty and dermatitis; the fruits, in quantity, intoxicate birds and cause fatal trauma in four-footed animals. The abundant nectar yields a spicy commercial honey and beekeepers are opposed to eradication programs (Crane, 1981).

TRADITIONAL MEDICINE

The Brazilian pepper tree is indigenous to South and Central America. In this area three different trees (*S. molle, S. aroeira*, and *S. terebinthifolius*) are all interchangeably called pepper trees (Campelo and Marsaioli, 1974). The berries of pepper trees are rich in essential oil, which imparts a peppery flavor, and are used in syrups, vinegar, and beverages in Peru as well as Chilean wines. In some countries, dried and ground berries are used as a pepper substitute or as an adulterant of black pepper (*Piper nigrum*). They have also been used in the perfume industry (Moneam and Ghoneim, 1986).

Medicinal plants have been used for centuries as an alternative treatment for health problems. Almost all parts of *S. terebinthifolius*, including leaves, bark, fruit, seeds, resin, and oleoresin (or balsam), have been used medicinally by indigenous peoples throughout the tropical regions. Leaf tea is used to treat colds, and leaf decoction is inhaled for hypertension, depression, and irregular heart beat. Decoction of the bark is used in baths to relieve rheumatic and back pain (Panetta and McKee, 1997). Traditionally, *S. terebinthifolius* was also used as an antibacterial, antiviral, diuretic, digestive stimulant, tonic, wound healer, anti-inflammatory, and hemostatic as well as a medicament to treat urinary and respiratory infections (Melo-Junior et al., 2002).

CHEMICAL COMPOSITION OF ESSENTIAL OIL

Essential oils were obtained by steam distillation or extraction by solvents from berries or leaves of *S. molle* and *S. terebinthifolius*. Among 57 and 62 compounds wereidentified in these oils, the main were α-phellandrene (46.52%) and 34.38%), β-phellandrene (20.81% and 10.61%), α-terpineol (8.38% and 5.60%), α-pinene (4.34% and 6.49%), β-pinene (4.96% and 3.09%) and *p*-cymene (2.49% and 7.34%), respectively. A marked quantity of γ-cadinene (18.04%) was also identified in the *S. terebinthifolius* essential oil whereas only traces (0.07%) were detected in the essential oil of *S. molle* (Bendaoud et al., 2010). Percentage distribution of the individual substances in the oil may differ from the source (El-Massry et al., 2009; Gundidza et al., 2009; Santos et al., 2009; Santana et al., 2012) and also seasonal effects were observed (Barbosa et al., 2007). Typical composition of essential oil from the leaves of Brazilian pepper tree is showed in Table I (Silva et al., 2010).

Essential oil of leaves can be used as an effective repellent and acted as hunger inhibitor in *Sitophilus oryzae* L., popularly known as weevils (Benzi et al., 2009). It also has insecticidal and repellent activity against *Trogoderma granarium*, known as insect pest of rice, and *Tribolium castaneum* - brown beetle, which attacks all types of ground cereals. Finally, the aqueous extract proved to be effective against *Candida albicans* (Ceruks et al., 2007).

Table I. Chemical compounds in leaf's Essentials oil from Brazilian pepper tree (According to Silva et al., 2010)

Compounds	**Relative percentage analyzed by GC/MS**
o-Cymene	1.7
Limonene	0.2
m-Cymenene	0.7
2,5-Dimethyl-styrene	1.0
Perillene	0.5
Myrcenol	0.8
α-Campholenal	0.8
trans-Limonene oxide	3.1
cis-Verbenol	0.9
trans-Verbenol	2.7
m-Cymen-8-ol	4.1
p-Cymen-8-ol	3.2
α-Terpineol	0.7
Verbenone	7.4
Carvone	7.5
α-Terpinen-7-al	1.9
p-Cymen-7-ol	22.5
β-dehydro-Eelsholtzione	4.6
α-Cubebene	0.3
neo-dihydro-Carveol acetate	0.5
β-Bourbonen	0.1
iso-Longifolene	2.7
cis-Muurola-4(14),5-diene	3.5
9-epi-(E)-caryophyllene	10.1
β-Chamigrene	1.0
γ-Himachalene	0.9
γ-Muurolene	1.8
α-Bulnesene	0.6
Spathulenol	0.6
Caryophyllene oxide	5.2
β-Eudesmol	1.0
α-Cadinol	0.6
Aristolone	2.3

CHEMICAL COMPOSITION OF TREE STEM BARK AND AERIAL PARTS

Extract from tree stem bark of *S. terebinthifolius* is widely used in Brazil as a topical antiinflammatory agent and to cicatrize wounds. The extract contains catechin, tannins, terpenes, flavonoids, and saponins (Borio et al., 1973; Morais et al., 2014). In these components, both mutagenic potential and antioxidant properties have been ascribed to flavonoids (de Carvalho et al., 2003).

Previous chemical studies with leaves extracts of *S. terebinthifolius* have been carried out and fatty acids and terpenoids were isolated, especially tirucallane derivatives (masticadienoic acid and schinol) which have shown inhibitory activity on phospholipase A2 (Jain et al., 1995) and antifungal potential against Paracoccidioides brasiliensis (Johan et al., 2010). Other compounds, such as phenolic derivatives (gallic acid, methyl and ethyl gallates) and flavonoids (trans-catechin, kaempferol, quercitrin, afzelin, myricetin, and myricetrin) were also isolated from the leaves and displayed antiradical and cytotoxic activities (Ceruks et al. 2007; Santana et al., 2010).

Similar terpenes were isolated from the bark resin of *Schinus molle* L. (germacrene-D, terebinthene, isomasticadienoic acid, isomasticadienonalic acid, and pinicolic acid). Among these compounds the sesquiterpene hydrocarbon terebinthene showed significant growth inhibitory activity against human colon carcinoma HCT-116 cells. Furthermore, terebinthene and pinicolic acid also showed antibacterial activity against *Staphylococcus aureus* ATCC 25923 and *Bacillus subtilis* ATCC 6633 (Malca-García et al., 2016).

From the aerial parts of *S. Terebinthifolius*. numerous bioactive compounds were isolated: flavonoids and biflavonoids (Yueqin et al., 2003), xanthones, hydroxychalcones, coumarins, 2,8-dihydroxyadenine, and some phenolic compounds (Queires et al., 2006) as for example anthocyanins, gallic acid, and tannins (galloyl glucoses, galloyl shikimic acids) (Hayash et al., 1989), and others.

PHARMACOLOGICAL AND BIOLOGICAL ACTIVITIES

Brazilian pepper tree is used as anti-rheumatic, anti-septic, anti-inflammatory, antifungal, antimicrobial, wound healing, in the treatment of disorders related to skin (Diaz et al., 2008) and in anti-depressive treatment (Machado et al., 2007).

The *in vitro* antioxidant and antiradical scavenging properties of the investigated essential oils were evaluated by using 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2,2′-Azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assays. Essential oil of *S. terebinthifolius* expressed stronger antioxidant activity in the ABTS assay, with an IC_{50} of 24 ± 0.8 mg/L, compared to *S. molle* (IC50= 257 ± 10.3 mg/L). Essential oils were also evaluated for their anticancer activities against human breast cancer cells (MCF-7). *S. terebinthifolius* essential oil was more effective against tested cell lines (IC_{50} = 47 ± 9 mg/L) than that from *S. Molle* (IC_{50} = 54 ± 10 mg/L).

Antibacterial and Antifungal Activities

S. terebinthifolius leaf essential oil has shown antibacterial activity against *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Shigella dysenteriae*, *Staphylococcus albus*, *Staphylococcus aureus* and *Staphylococcus intermedius* as well as antifungal activity against *Aspergillus niger*, *Aspergillus parasiticus* and *Candida albicans* (El-Massry et al. 2009; Silva et al. 2010). Extracts from *S. terebinthifolius* leaves in ethanol and dichloromethane containing secondary metabolites such as phenols, flavones, flavonoids, xanthones, leucoanthocyanidins, flavanones and free steroids were active against *E. coli*, *Ps. aeruginosa*, *Staph. aureus* and *C. albicans* (de Lima et al. 2006; El-Massry et al. 2009). Among 23 extracts from 12 plants, an aqueous extract from the leaves of *S. terebinthifolius* showed the highest activity against *Staph. aureus*, and it could inhibit the growth of *B. subtilis* (Martinez et al. 1996).

In other laboratory tests, the essential oil, as well as leaf and bark extracts of *S. terebinthifolius*, has demonstrated potent antimicrobial properties (Ghanney and Rhouma, 2015). On the antibacterial effect of pepper involved terpene compounds, but also other substances (Johan et al., 2010), including high molecular compounds (Gomes et al., 2013). Brazilian pepper tree has displayed good-to-very strong in vitro antibacterial activity against numerous bacterial strains and antifungal actions against numerous fungi, as well as *Candida* (Leite et al., 2011; Correia et al., 2016). The aqueous extracts of *S. terebinthifolius* showed antifungal activity against *Candida albicans* with MIC of 120 ng/ml (Schomourlo et al., 2005).

Anti-adherent Activity

Crude methanol, and acetate-methanol extracts from *S. terebinthifolius* demonstrated inhibition of *Streptococcus mutans* and *Candida albicans* on in vitro biofilm formation. The biofilms of *C. albicans* were more efficiently inhibited by the *S. terebinthifolius* fraction of acetate–methanol and methanol in hydroalcoholic solvents ($p < 0.05$).

This experiment suggested the importance of studies about these extracts for therapeutic prevention of oral diseases associated with oral biofilms (Barbieri et al., 2014).

Anti-inflammatory Activity

The anti-inflammatory potential was evaluated based on the ethnopharmacological use of *S. terebinthifolius* focusing on two important aspects: the inhibition of NO production by macrophages, and the ability to scavenge free radicals (da Silva Dannenberg et al., 2016). The hydroalcoholic extract from *S. terebinthifolius* leaves exhibited important anti-inflammatory properties in pleurisy and arthritis, including a marked inhibition of neutrophil influx and reduced inflammatory mediators induced by zymosan (Rosas et al., 2015). Many experiments showed that S. *terebinthifolius* may have potential as a phytomedicine for the treatment of inflammatory conditions (Uliana et al., 2016).

Antioxidant Activity

The antioxidant activity of *S. terebinthifolius* may be related to the presence of polyphenols in leaves and fruits essential oil. In fact, phenolic phytochemicals are thought to promote optimum health partly via their antioxidant and free radical scavenging effects thereby protecting cellular components against free radical induced damage. The methanol extract of *S. terebinthifolius* showed protection against enzymatic and non-enzymatic lipid peroxidation in microsomal membranes of rat. Besides, this extract exhibited the highest scavenging activity on the superoxide and DPPH radicals (Velázquez et al., 2003). Essential oil from *S. terebinthifolius* showed strong antioxidant activity in the ABTS assay (IC_{50} = 24 mg/L) (Bendaoud et al., 2010). Ethanolic extract of *S. terebinthifolius* showed significant activity against DPPH radical at 200 mg/ml with 92.8 % inhibition (Youssef Moustafa et al., 2010). The results of the work do Rosário Martins et al. (2014) showed that essential oils of leaves and fruits demonstrated antioxidant and antimicrobial properties, suggesting their potential use in food or pharmaceutical industries.

Cytotoxic Activity

The crude essential oil from leaves showed cytotoxic effects in several cell lines, mainly on leukemia and human cervical carcinoma. Fractions composed mainly of α- and β-pinenes as well as those composed of individually pinenes showed effective activities against all tested cell lines (Santana et al., 2012). The turucallane triterpenoids ((Z)-masticadienoic and (E)-masticadienoic acids and (Z)-schinol), isolated from leaves of *S. terebinthifolius*, as well as some semi-synthetic derivatives were cytotoxic and demonstrated antiparasitic (antileishmanial and antitrypanosomal) activity (Morais et al., 2014). Crude hydroethanolic extract from the stem bark of *S. terebinthifolius*, as well as its fractions and isolated compounds, showed anti-HSV-1 (Herpes simplex virus type 1) activity and exhibited potential for future development treatment against orofacial infections associated with HSV-1 (Nocchi et al., 2016).

Antitumor Activity

Anticancer properties of essential oil from berries of *S. terebinthifolius* were evaluated against human breast cancer cells (MCF-7) revealing that *S. terebinthifolius* essential oil was effective against tested cell lines (IC_{50} = 47 mg/L) (Bendaoud et al., 2010). Ethanolic extract of *S. terebinthifolius* showed significant activity against acetylcholinesterase and butyrylcholinesterase with 75.4 and 100 % of inhibition respectively at 1 mg/ml (Youssef Moustafa et al., 2007). Polyphenols extracted from *S. terebinthifolius* strongly inhibited androgen-insensitive DU145 human prostatic cell line proliferation in a dose-dependent manner. The results suggest that these polyphenols induce apoptotic and autophagic cell death (Queires et al., 2006).

Antiulcerogenic Activity

Water extract of the bark of *S. terebinthifolius* showed a marked protective effect against gastric ulcerations induced by immobilization stress at low temperature in rats. The antiulcer effect was accompanied by increase in volume and pH of the gastric juice, and by reduction in bleeding (Carlini et al., 2010).

TOXICOLOGY

The acute and subacute administration of the dried extract of *S. terebinthifolius* bark did not produce toxic effects in Wistar rats. In the acute toxicity test, bark extract did not produce any toxic signs or deaths. The subacute treatment with *S. terebinthifolius* did not alter either the body weight gain or the food and water consumption. The hematological and biochemical analysis did not show significant differences in any of the parameters examined in female or male groups, except in two male groups, in which the treatment with *S. terebinthifolius* (0.25 and 0.625 g/kg) induced an increase of mean corpuscular volume values (2.9 and 2.6 %, respectively). These variations are within the physiological limits described for the specie and does not have clinical relevance (Lima et al., 2009).

The preclinical toxicity was tested in male rats (17.6 mg/kg) in 83 days chronic treatment and a reduction in the number of red blood cells and hemoglobin was seen following administration of *S. terebinthifolius*. The mating ability and fertility were not affected. Moreover, bone malformations were induced in fetuses, and a slight delay in recovery time of the postural reflex was observed in pups from female animals treated (18 days) with *S. terebinthifolius*. Given these results, a better assessment of the risks and benefits of the internal use of these plants is necessary, especially when used by women of childbearing age (Carlini et al., 2013).

The water extract from the bark of *S. terebinthifolius* was negative in a cell-freeplasmid DNA test, indicating that it did not directly break DNA. On the other hand, positive results were obtained in the SOS chromotest, in a forward mutagenesis assay employing *E. coli*, and in the *Salmonella* reversion assay. The results indicated that Brazilian pepper tree extract produces DNA damage and mutation in bacteria, and that oxidative damage may be responsible for the genotoxicity (Carvalho et al., 2003).

CONCLUSIONS

The genus Schinus is widespread all over the Americas, Europe and Africa, and many species of this genus have been used as traditional herbal medicines. The chemical investigation of Schinus species has revealed many secondary metabolites from this genus with significant bioactivities. Bioactive components include monoterpenes, sesquiterpens, triterpenes, fatty acids and flavoinoids. On account of the presence of these compounds significant antifungal, analgesic, antioxidant, antitumor, insecticidal activities of extracts obtained from the plants of the genus have been reported in the literature. Nevertheless, there are only a few Schinus species that have been studied in detail.

Specimens of *Schinus terebinthifolius,* known in Brazil as "aroeira-vermelha" or "aroeira-pimenteira", are large trees that can reach 40 m height and 1–3 m in diameter . In folk medicine, this plant has been used to treat ulcers, respiratory problems, wounds, rheumatism, gout, diarrhea, skin disease and arthritis, it is also antiseptic and anti-inflammatory. In addition, decoctions of flowers, stems, leaves and fruits are used for the treatment of tumors. *S. terebinthifolius* is a Brazilian plant that produces great amounts of biologically active compounds, many of which could also find its place in modern medicine.

Competing interests

The authors declare that they have no competing interests.

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