BJNS
Brazilian Journal of Natural Sciences

Brazilian Journal of Natural Sciences

www.bjns.com.br

ISSN 2595-0584 - V.3 N.1
March 2020 - pag. 249 - 258
Electronic journal

Review Article

MELALEUCA SPP ESSENTIAL OIL AND ITS MEDICAL APPLICABILITY. A BRIEF REVIEW

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Abstract

Medicinal plants have long been used as an alternative in the treatment of diseases, whether using extracts, essential oils and / or bioactive components. Thus, the use of medicinal plants, with popularly known effects for the treatment of infections, has gained prominence, in research related to extracts and essential oils of medicinal plants, in an attempt to discover and future application of new molecules with antimicrobial and / or effect coadjuvant molecules to antimicrobials on the market. Studies with species of *Melaleuca spp.*, Demonstrate wide application of its essential oil, without treating skin infections, microbial infections, herpes, diseases associated with pathogenic microorganisms of the oral cavity. The emerging microbial resistance to the drugs currently available on the market, has been affected by both researchers and the general population, so that the research experimented with was conducted revealing a high synergistic potential between drugs and natural drugs, present in drugs. In view of the above, this study aimed to present, through a bibliographic survey, a use of medicinal plants in the face of microbial resistance, as well as medicinal therapy based on the use of essential oils from *Melaleuca alternifolia, Melaleuca leucadendron and Melaleuca quinquenervia, already inclusion in the literature.*

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DOI: https://doi.org/10.31415/bjns.v3i1.89 - Article received on: February 28, 2020; accepted February 29, 2020; published on March 10, 2020. Brazilian Journal of Natural Sciences, Vol. 3, N.1, March 2020. Available online from March 10, 2020, ISSN 2595–0584. www.bjns.com.br. All authors contributed equally to the article. The authors declare that there is no conflict of interest.

Resumo

Plantas medicinais há muito vêm sendo empregadas, como alternativa no tratamento de doenças, quer pelo uso de extratos, de óleos essenciais e/ ou respectivos componentes bioativos. De tal forma, a utilização de plantas medicinais, com efeitos popularmente conhecidos para tratamento de infecções, ganhou destaque, em pesquisas envolvendo extratos e óleos essenciais de plantas medicinais, na tentativa da descoberta e, futura aplicação, de novas moléculas com efeito antimicrobiano e/ou moléculas coadjuvantes aos antimicrobianos existentes no mercado. Estudos com as espécies de *Melaleuca* spp., têm demonstrado ampla aplicabilidade de seu óleo essencial, no tratamento de infecções de pele, infecções microbianas, herpes, inclusive doenças associadas a microrganismos patogênicos da cavidade oral. A emergente resistência microbiana aos fármacos disponíveis atualmente no mercado, tem preocupado tanto aos pesquisadores, quanto a população em geral, de tal forma, que as atuais pesquisas têm sido conduzidas revelando um elevado potencial sinérgico entre os fármacos e compostos naturais, presentes em óleos essenciais. Diante do exposto, este trabalho teve por objetivo apresentar, por meio de levantamento bibliográfico, a utilização de plantas medicinais frente a resistência microbiana, bem como a terapêutica medicinal a partir do uso dos óleos essenciais de *Melaleuca alternifolia*, *Melaleuca leucadendron* e *Melaleuca quinquenervia,* já descritos na literatura.

Introduction

The use of therapeutic plants in medicines has been practiced for thousands of years, being used by most people in the world. The knowledge acquired over time about the use of plants by these peoples has been passed down from generation to generation and is still used today. In the present time, the use of plants as therapeutic alternatives has helped some populations that do not have access to modern treatments and high cost drugs, thus, the use of plants for the treatment of diseases has been empirically used in a widespread way. In recent years, with the scientific advancement, the development of research on this subject has helped to prove the activity of these plants aiming at the search for new compounds with therapeutic properties, allowing the empirical use of plants to make room for scientific foundation. (Cechinel Filho & Yunes, 1998; Santos et al., 2009; Oliveira et al., 2007).

Scientific studies involving the use of medicinal plants and herbal action have already contributed to obtain various drugs used in traditional medicine (Veiga Jr et al., 2005; Cechinel & Yunes, 1998). In Brazil, studies on medicinal plants are of great importance, especially for the encouragement and appreciation given by the Ministry of Health, with incentive programs with the basic health units in the country. In the Dental area, Phytotherapy is already an integrative and complementary practice to oral health (resolution CFO-082/2008), and its recognition is a great step to regulate the use and performance of the dental surgeon in this area. Studies showed that plant-derived oils and extracts were effective in antimicrobial control, including oral cavity colonizers (Cecanho et al., 1999; Duarte et al., 2004; Buso- Ramos, 2018; Barbosa, 2018; Puppin, 2018; Barbosa et al, 2019; Höfling et al., 2019; Oliveira, 2019). Another alternative for the use of medicinal plants has been the synergistic combination with other existing commercial medicines, in an attempt to reduce or avoid the side effects of conventional medicines. Some reports in the literature indicate that plant derivatives may enhance the efficacy of traditional medicine. Studies point out that some essential oils and phytochemicals have synergistically improved activities with commercial antifungals.

Medicinal plants and microbial resistance

Microbial resistance refers to the ability of a microorganism to withstand a given antimicrobial treatment. Infections caused by multiresistant bacteria and fungi has become a challenge for the control of infectious diseases (Souli et al., 2008). Despite the range of antimicrobials available to control these microorganisms, both fungi and bacteria have developed molecular strategies for the expression of resistance to existing drugs. The resistance of organisms against antimicrobial drugs has become a major problem, especially when it comes to infections in immunocompromised patients. Such evidence has resulted in a drastic increase in the incidence of systemic and opportunistic microbial infections, which leads to a growing need for the development of effective new drugs (Gonçalves, 2016).

Due to multidrug resistance, pharmaceutical companies have sought to develop new antimicrobial agents to combat these bacteria. The search for new drugs derived from medicinal plants has been the target of several studies aiming at producing new drugs to reduce side effects, lower toxicity with lower resistance index and greater spectrum of action (Al-Mariri, 2013; Alvarenga et al., 2007, Sardi et al., 2013). As a result, research on plant species has been important to the discovery of a new antimicrobial compounds that will be of great importance due to the numerous reported cases of drug resistance (Sartoratto et al., 2004).

The use of plants as a source of natural derivatives plays an important role in the development of tools for the treatment of diseases, as well as the confirmation of their action potential with literary findings, which showed in vitro antifungal and antibacterial activity of plant extracts and essentials oils.

Essential oils are a rich source of biological active compounds, chemically derived from the secondary metabolism of plants, and their properties have been widely known since ancient times. (Castro & Lima, 2010; Saad et al., 2010; Tempone et al., 2008). Thus, the discovery and use of natural products with antifungal activity may represent a new tool for the production and use of herbal medicines to combat infectious agents (Khan, et al., 2012; Mendes, 2011; Silva, et al., 2009, Abrantes et al., 2013; Buso- Ramos, 2017; Barbosa, 2018; Puppin, 2018; Barbosa et al, 2019; Hofling 2019; Oliveira, 2019). Therefore, research with medicinal plants, such as *Melaleuca* spp., has contributed to the discovery of new compounds with antimicrobial potential, associated with the increase of resistance cases showed by some microorganisms, justifying research with this plant in search of new sources of antimicrobial drugs action.

***Melaleuca* spp.**

Melaleuca spp. is a plant used by traditional Australian medicine. It belongs to the *Myrtaceae* family, composed of at least 3,000 species in 130-150 genera, widely distributed in tropical and warm climate regions of the world. *Melaleuca* species are included in the *Myrtaceae* family, which originated in Australia and was spread throughout Southeast Asia, including Indonesia. These plants are well adapted to acidic, soggy, and moderately saline soils (Doran & Turnbull, 1997; Kaufman & Smouse, 2001).

They are essential oil producers by secretory glands in the subdermal regions of the leaves. It is composed of terpene hydrocarbons, mainly monoterpenes, sesquiterpenes and their associated alcohols. The essential oil produced and known for its anti-inflammatory and antimicrobial properties (Saller et al., 1998) has chemical compounds such as terpinen-4-ol, terpinene, cineol, terpinolene, cymene, pinene, limonene, sabinene, glubulol and viridiflorol, Its composition exhibits mostly terpene compounds (Brophy et al., 1989; Southwell & Stiff, 1989; Buck et al., 1994), known to destabilize cell envelopes of microorganisms, causing cell membrane lysis. Thus, of all activities associated with oil, the antimicrobial activity is the most recognized, due to studies already found in the literature.

Melaleuca alternifolia

Melaleuca alternifolia (TTO), Chell is a plant used by traditional Australian medicine. Its essential oil is produced by secretory glands in subdermal regions of leaves showing in its constitution chemical compounds such as terpinen-4-ol, terpinene, cineol, terpinolene, cymene, pinene, limonene, sabinene, glubulol and viridiflorol, its composition exhibits mostly terpenic compounds (Brophy et al., 1989; Southwell & Stiff, 1989; Buck et al., 1994). Its topical use is widespread in Australia, the United Kingdom, Italy and Brazil for its broad medicinal properties,

with gels, soaps and creams being their most common means of application.

Pharmacological activities include antimicrobial potentials (Mondello et al., 2003; Silva et al., 2003; Carson, Hammer and Riley, 2006; D'Arrigo et al., 2010), antifungal (Hammer, Carson and Riley, 1999; Bagg et al., 2006), antiviral (Carson and Riley, 1993, 1994, 1995; Lis-Balchin, Hart and Deans., 2000; Gruenwald, Brendler and Jaenicke., 2000; Garozzo et al., 2011), in addition to its use in the treatment of skin problems such as infections (Carson, Hammer and Riley, 2006), herpes simplex (Budhiraja et al., 1999) and dental use (Oliveira et al., 2011), among others.

Several therapeutic properties are attributed to *M. alternifolia* essential oil, among which the most cited are antibacterial, antifungal, antiviral, anti-inflammatory and analgesic activity (Peña, 1962; Tong et al., 1992; Carson and Riley, 1993; Buck et al., 1994; Hammer et al., 1996; Hammer et al., 1997).

It has also been reported to be used for the treatment of *Tinea pedis* and *onychomycosis*. Studies have successfully described the use of the oil in the treatment of mucosal infections such as *Trichomonas vaginalis* (Peña, 1962), oral bacteria, and oropharyngeal candidiasis (Jandourek et al., 1998; Groppo et al., 2002; Walker, 1972; Tong et al., 1992; Buck et al., 1994; Syed et al., 1999; Satchell et al., 2002). Among them, the one that attracts the most attention is its antibacterial activity where researchs showing its broad spectrum of action against bacteria and its activity against methicillin resistant *Staphylococcus aureus* strains (Carson et al., 1995; Carson et al., 1996; Hammer et al., 1996; Carson et al., 1998; Halcon and Milkus 2004, Carson 2006; Falci et al.,2015, Oliveira et. al., 2016).

Different studies have been performed showing a variety of transient skin microorganisms with susceptibility to essential oils, which even with the use of this oil, provides the maintenance of the microbiota, acting as a barrier against the colonization of pathogens (Hammer et al., 1996; Carson and Riley, 1998; Banes-Marshall et al., 2001; Halcon and Milkus, 2004). Studies also demonstrate activity against *Streptococcus pyogenes* (Carson et al., 1996), β-*hemolytic streptococci, Pseudomonas aeruginosa* (Banes-Marshall et al., 2001; Halcón and Milkus, 2004), kanamycin resistant *enterococci, Acinetobacter baumannii, Escherichia coli* and *Klebsiella pneumoniae* (Carson and Riley, 1995; Carson et al., 1995; Hammer et al., 1996; Nelson, 1997).

Benger et al. (2004) showed the value of 0.1% of the essential oil as a fungistatic concentration for *Tricophytum rubrum*. Hammer et al. (1998) and Carson et al. (1998) also found in clinical isolates of different *Candida* spp and some reference strains, their susceptibility to oil at dilutions less than or equal to 0.5%. The ability to promote *in vitro* differentiation of monocytes has also been demonstrated (Budhiraja et al., 1999). Anti-inflammatory properties contribute to the healing of chronic wounds based on suppression of inflammatory mediator production by monocyte activation (Finlay-Jones et al., 2001; Hart et al., 2000, Koh et al., 2002; Halcón and Milkus, 2004).

Melaleuca leucadendron

Melaleuca leucadendron Linn. is the most cultivated specie in Indonesia, known by the name of "Kayu Putih". In Indonesia, *M. leucadendron* Linn. is mainly grown in natural forests and plantations. This plant is usually found in Java Island, Maluku, Nusa Tenggara Timur and Sulawesi Island. *Melaleuca leucadendron* Linn. It was planted in Ponorogo of Java for the first time and distributed to Gunung Kidul in Yogyakarta and other areas such as Gundih and Surakarta in Central Java, Mojokerto and Sukun in East Java, and Cikampek, Majalengka and Indramayu in West Java. Over the past four decades, forest owners have explored the leaves of Java plantations.

Cashew oil is used in combination with a large number of other plant drugs and medicinal plants, such as *eucalyptus* and mint essential oils, reflecting various uses and indications (Blumenthal et al., 1998). Cajeput essence is used as a urinary antiseptic (Moreira Filho and Goltcher, 1972 apud Fenner et al. 2006).

There are also other unproven uses: its use for muscle and joint pain in rheumatic diseases, sciatica, low back pain, disc dislocation and low back pain. The oil is also used for muscle tension and pain after sports injuries such as sprains, bruises and stretching of the muscles or ligaments (Gruenwald, Brendler and Jaenicke, 2000).

Other indications and uses include the treatment of rheumatism, neurogenic pain, temporary relief of muscle pain, tendency to infection, wounds, burns and tonic function (Brophy et al., 1989; Johns

and Rudolph, 1992; Leach et al., 1993; Gruenwald, Brendler and Jaenicke, 2000; Monteiro et. al., 2013).

Melaleuca quinquenervia

Melaleuca quinquenervia is an exotic, invasive tree from Australia belonging to the *Myrtaceae* family. It proliferates rapidly, producing large amounts of seeds, adapted to both dry and flooded areas. The species was introduced to the United States in early 1886 as an ornamental plant and also to help dry out marshy areas (Dray Jr. et al., 2004).

Melaleuca quinquenervia is a small to medium tree 4 to 12 m high, with exceptional specimens reaching 25 m (Boland et al., 1984). This species typically occurs in low-lying, seasonally flooded habitats along the east coast of Australia, ranging from Towra Point (Botany Bay) in New South Wales to Cape York Peninsular in Queensland extending south of New Guinea. It is also found in New Caledonia, where extensive settlements occur on well-drained slopes and ridges, especially in the northwestern part of the island. The species has been planted in tropical lowlands in several countries where it supplies fuel, wood, flowers for honey production and leaf essential oil (Doran and Turnbull, 1997, Doran and Turnbull, 1999).

M. quinquenervia is a member of broadleaf *Melaleuca* group, known as the *Melaleuca leucadendra* alliance (Blake, 1968). The alliance is a complex of 15 species, including those known as *Melaleuca cajuputi* Powell, *M. leucadendra* L. and *Melaleuca viridiflora* Sol. Ex Gaertner and *M. quinquenervia*. These species, however, were previously combined under the name of *Melaleuca leucadendron* L. (Craven, 1999). Reports of *M. quinquenervia* essential oil chemistry may therefore appear under various names and often under that of his close relative. *M. viridiflora* (Blake, 1968). Plants identified as *M. viridiflora* in literature prior to 1968, which are outside their natural distribution from tropical regions in Western Australia, the Northern Territory and Queensland, are probably *M. quinquenervia*.

Some of the *M. quinquenervia* leaf essential oils are of commercial interest. *M. quinquenervia* leaves are a rich source of 1,8-cineol essential oil called Niaouli oil, which is used in pharmaceutical preparations for the relief of coughs and colds, rheumatism, neuralgia, and aromatherapy. They have *in vitro* antibacterial action and stimulate circulation (Blumenthal et al., 1998; Gruenwald, Brendler and Jaenicke, 2000), upper respiratory tract secretion (Blumenthal et al., 1998), treatment of cough and bronchitis (Gruenwald, Brendler and Jaenicke, 2000). Unproven uses include oil for rheumatism, neuralgia and cystitis.

M. quinquenervia has been reported to occur in two distinct chemical forms or "chemotypes". Chemotype 1 is characterized by acyclic leaf terpenes, in particular high concentrations of sesquiterpene Nerolidol (74-95% of the total oil), and monoterpene linalol (Ireland et al., 2002, Wheeler et al., 2007). Chemotype 2 contains high concentrations of cyclic leaf terpenes, especially sesquiterpene viridiflorol (13-66% of total oil), and monoterpenes 1,8-cineol and α-terpineol (Ireland et al., 2002, Wheeler et al., 2007).

The composition of the essential oil of *Melaleuca quinquenervia* (*Myrtaceae*) varies widely (different chemotypes). The main components listed for this oil are E-nerolidol and viridifloral, which have distinct biological properties (Padovan et al. 2010; Santiago et al., 2018).

***Melaleuca* essencial oil in researches against microrganisms**

The literature reports the proven effectiveness of TTO in wound healing, promoting skin revitalization (Mertas et al, 2015). A study by Chin and Cordell (2013) tested TTO in patients with wounds infected with *Staphylococcus aureus*. As a result, accelerated healing was observed in patients who used the oil and total revitalization of the injured skin, noting also the reduction of bacteria that infected the wounds.

TTO is an excellent bactericide. Some research has demonstrated the effectiveness of this oil against different strains of bacteria, such as *Staphylococcus aureus, Legionella pneumophila* and *Staphylococcus aureus* (Amri et al, 2012).

Tea tree oil is also used in products in dentistry, mainly those intended to reduce plaque, gingivitis, periodontitis and dental caries. *In vitro* evidence has shown that *Melaleuca alternifolia* has bactericidal and bacteriostatic effects against the most prevalent periodontopathogens. Clinical studies have found effects in the reduction of gingival inflammation, antiplaques, beneficial antioxidant properties for the host and reduced immunoinflammatory responses to pathogens (Santamaria et al, 2014; Graziano et al,

2016; Casarin et al, 2018; Oliveira, 2019).

Melaleuca oil has showed good antibacterial action *in vitro* against microorganisms on the skin surface, oral cavity and its action against microorganisms with multidrug resistance, however, studies of its mechanism of action on microbial cells, studies in vivo, and its cytotoxic activity still they are necessary, since their applicability has been spreading to the areas of dentistry, be it in the chemical maintenance of hygiene or prevention of oral diseases, cleaning after skin cleansing and even after podiatry procedures.

Conclusion

The essential oil of *Melaleuca* spp. it can be an important ally of current medicine in combating multidrug-resistant pathogens. Being a plant essential oil, it is a natural treatment and when used correctly it presents a more specific and less aggressive therapeutic activity to the health of compromised patients.

The essential oil has been shown to be effective against several pathogenic microorganisms resistant to conventional drugs. Despite its geographical location, the extraction of this essential oil has in its composition, mainly terpinene-4-ol, a compound already described in the literature with antimicrobial properties that characterize the activity of this essential oil. However, the isolated composition of these components needs to be studied regarding to its mechanisms of action and description of the morphological impairment of these microorganisms. This review highlights the main therapeutic applications of this essential oil and stimulates further studies on the therapeutic employability of the essential oil of *Melaleuca* spp.

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