REVISTA Fitos®

REVISÃO
FARMACOLOGIA

Purified bioactive compounds from *Mentha* spp. oils as a source of Candidosis treatment. A brief review

Compostos bioativos purificados de óleos de *Mentha* spp. como fonte de tratamento de candidose. Uma breve revisão

DOI 10.5935/2446-4775.20170009

[1]BONI, Giovana C.*; [1]FEIRIA, Simone N. B. de; [1]HÖFLING, José F.

[1]University of Campinas - UNICAMP, Piracicaba Dental School, Piracicaba, SP, Brazil.

*Correspondência: giovanac.boni@gmail.com

Abstract

Medicinal plants have been the subject of many studies in an attempt to discovery alternative drugs, since they are sources of potentially bioactive compounds that may act in the maintenance of human health. The discovery of new antimicrobial substances or biocomponents derived from natural products has been important in the control of microorganisms, especially due to the increase of cases of resistance to conventional antimicrobials. In parallel, yeasts of the genus *Candida* are becoming a public health problem in the last decades due to the increase of infections denominated candidosis. *Candida* spp. has mechanisms of virulence, such as polymorphism and biofilm formation, that facilitate the development of the infection and difficult the treatment. In this sense, studies found in the literature with bioactive compounds from *Mentha* spp. essential oil, describe their antifungal action, especially from the isolated compounds as carvone, mentone, menthofuran and pulegone. In this sense, this review describes studies about antimicrobial activity of these compounds especially against yeasts of *Candida* species and some particularities of this genus such as virulence mechanisms once these themes are crucial for the development of new alternative drugs and/or antifungal agents that may act as adjuncts to conventional treatments against these microorganisms.

Keywords: *Candida* spp. *Mentha* spp. Carvone. Menthone. Menthofuran. Pulegone.

Resumo

Plantas medicinais têm sido objeto de muitos estudos na tentativa de descobrir drogas alternativas, uma vez que são fontes de compostos potencialmente bioativos que podem atuar na manutenção da saúde humana. A descoberta de novas substâncias antimicrobianas ou biocomponentes derivadas de produtos naturais tem sido importante no controle de microrganismos, especialmente devido ao aumento de casos de resistência a antimicrobianos convencionais. Em paralelo, leveduras do gênero *Candida* vem se tornando um problema de saúde pública nas últimas décadas, devido ao aumento de infecções

denominadas candidoses. *Candida* spp. possuem mecanismos de virulência, como polimorfismo e formação de biofilme, que facilitam o desenvolvimento da infecção e dificultam o tratamento. Nesse sentido, estudos na literatura com compostos bioativos do óleo essencial de *Mentha* spp. descrevem sua ação antifúngica, especialmente dos compostos isolados como carvona, mentona, mentofurano e pulegona. Sendo assim, esta revisão teve como objetivo abordar estudos sobre a atividade antimicrobiana destes compostos especialmente contra leveduras do gênero *Candida* e algumas particularidades desse gênero, tais como mecanismos de virulência, uma vez que esses temas se tornam cruciais para o desenvolvimento de novas drogas alternativas e/ou agentes antifúngicos que possam atuar como adjuvantes aos tratamentos convencionais contra esses microrganismos.

Palavras-chave: *Candida* spp. *Mentha* spp., Carvona, Mentona, Mentofurano, Pulegona.

Introduction

Fungal infections affect many peoples worldwide every year (BROWN et al., 2002). Due to the emergence and propagation of resistant microorganisms to conventional antifungal agents, the establishment of infections without possible treatments has affected especially the population of immunocompromised individuals, becoming a public health problem in the last decades (TSANG, BANDARA and FONG, 2012; LEWIS, 2013).

In the last years, it has been observed the increase of fungal infections with high morbidity and mortality. Technological advances for the treatment of diseases such as transplants, especially bone marrow, the advent of AIDS, anti-cancer chemotherapy and the widespread use of broad-spectrum antibiotic therapy are some factors associated to this phenomenon, contributing to the increase in the number of immunosuppressed patients susceptible to such infections (JABRA-RIZK, FALKLER and MEILLER, 2004). Therefore, pathogenic fungi have been target of research with the purpose to understanding virulence factors, pathogenesis of infections, and to discover more treatments that are effective. With the increased use of antifungals for bacterial infections, fungi have rapidly developed resistance to the various available drugs, particularly the yeasts of genus *Candida*. Therefore, due to the necessity of alternative sources of treatment, plants with antimicrobial potential have been the target of many researches for the purpose of discovering effective compounds against resistant organisms, with low toxicity to the host.

The use of medicinal plants in the form of purified extracts, oils or bioactive compounds as preventive therapy or alternative treatment, has evolved in recent years, promoting beneficial outcomes. (LORENZI and MATOS, 2002). The commercialization of medicinal plants is easily accessible to the population due to the "natural" concept attributed to them, characterized as a healthy product, safe and beneficial in the viewpoint of the population. However, the indiscriminate use of plants or their products, without pharmacological tests, preclinical and clinical studies, may result health damage such as toxic and allergic reactions, interactions with synthetic drugs, and synergistic effects, being a meticulous study before consumption by population is of great importance (VEIGA JR. and PINTO, 2005). An example of such effects is the therapeutic use of *Mentha pulegium* essential oil. The oral use of this essential oil in concentrations equivalent to 5 grams may result abortive and hepatotoxic action (LORENZI and MATOS, 2002).

Among the medicinal plants, the *Mentha* genus of the Lamiaceae family has been reported as of clinical relevance due to the presence of bioactive compounds, which have been extensively studied showing antibacterial, antiviral and antifungal activity (SAHARKHIZ et al., 2012). Plants of this genus have in their aerial

part structures called glandular trichomes, responsible for the secretion of essential oil containing bioactive compounds (MORAIS, 2009).

Studies have shown that purified chemical compounds as carvone, menthone, menthofuran and pulegone present in the essential oil of some *Mentha* species has demonstrated antibacterial and antifungal activity (MKADDEN et al, 2009; SAHARKHIZ et al, 2012; JALILZADEH and MAHAM, 2015). However, much work is still necessary to elucidate the antimicrobial effect of *Mentha* species against different species of microorganisms. Therefore, the objective of this brief review is to review the antimicrobial activity of isolated *Mentha* spp. compounds, such as carvone, menthone, menthofuran and pulegone especially against yeasts of *Candida* spp. and some particularities of this fungi genus, such as virulence mechanisms.

Candida spp. and virulence mechanisms.

Yeasts of the genus *Candida* are individual cells of rounded or oval shape, which measure approximately 2.0 to 6.0 µm. As cultural characteristics, the colonies are white to cream, with smooth or rough surface. They grow under aerobic or microaerobic conditions and reproduce asexually by budding. (SCHULZE and SONNENBORN, 2009).

Some species of *Candida* spp. reside in humans as commensal organisms of the microbiota in a large part of the population of healthy individuals without causing damage to health (SARDI et al., 2010; NAGLIK, CHALLACOMBE and HUBE, 2003). However, may cause fungal infections called candidosis, frequently associated with immunosuppressive states. Some factors considered predisposing to the disease are advanced age, nutritional deficiency, HIV, frequent exposure to antimicrobials and chemotherapeutic treatment (SARDI et al., 2010; ASMUNDSDÓTTIR et al., 2009; MONTERO et al., 2012).

In dentistry, *Candida* species has a relevant role in the development of oral infections and were identified mainly in immunocompromised patients (MIZIARA, LIMA and CORTINA 2004). *Candida albicans* is the most commonly opportunistic pathogen found in the oral cavity, and may cause superficial and systemic fungal infections (DAVEY and COSTERTON, 2006). Superficial infections affect the skin and mucosa. In systemic infections, the fungus can spread through the bloodstream and infect the internal organs (CALDERONE and FONZI, 2001). *Candida albicans* is considered the specie most prevalent in infections, however, *Candida parapsilosis*, *Candida tropicalis*, *Candida glabrata*, *Candida krusei*, *Candida guilliermondii* and *Candida lusitaniae* has also been highlighted in studies, being of great clinical interest (WEEMS, 1992; NAVES et al., 2013; MONTERO et al., 2012).

Candida spp. have a series of mechanisms of virulence that contribute to adaptation and proliferation in the human body and, later, the establishment of infections. One of these mechanisms is the ability of morphological transition by which the cell from the yeast form can form filaments. This transition is called polymorphism and have an important role in the processes of *Candida* spp. infection (SUDBERY, 2011).

These morphological transitions can happen due to environmental modifications such as pH changes and exposure to blood serum (GOW and HUBE, 2012; VYLKOVA et al., 2011; JACOBSEN et al., 2012). The germinative tube of *Candida* spp., marks the start of the hyphae growth (ELLEPOLA and SARAMANAYAKE, 2001). Among the events of budding, germ tube formation and formation of true hyphae, the fungus can still form pseudohyphas (CONSOLARO et al., 2005). The different forms that the fungus show is significant for pathogenicity and are involved in infection process (MAYER, WILSON and HUBE, 2013). The yeast form is

associated with the dissemination of the fungus and the filamentous form with the tissue invasion (JACOBSEN et al., 2012; NAVES et al., 2013; MAYER, WILSON and HUBE, 2013; HOGAN and SUNDSTRON, 2009). It is believed that the hyphae penetrate in the tissue through the combination of physical forces exerted by the extension of filaments and by the secretion of aspartyl proteinases enzymes expressed in the cell wall that help in the invasion process of the tissue. These, induce the hydrolysis of peptide bonds of host cells and facilitate colonization and infection in different tissues (WÄTCHLER et al., 2012; ZORDAN and CORMACK, 2012).

"Quorum sensing", an intercellular chemical communication mechanism through signaling molecules expressed by microorganisms stimulate several virulence factors among them the expression of polymorphism and biofilm formation (TSANG, BANDARA and FONG, 2012; JACOBSEN et al., 2012; NAVES et al., 2013). In *C. albicans* the main quorum sensing molecules are farnesol, tyrosol and dodecanol (BERMAN and SUDBERY, 2002).

Other important virulence factor is the biofilm formation ability (TSANG, BANDARA and FONG, 2012). *Candida* species can also be commonly found in biofilms. These biofilms represent the reduction of susceptibility of microorganisms to the action of most antimicrobial agents, contributing to the permanence of the infection (CHANDRA and MUKHERJEE, 2015). Among the many benefits to microorganisms present in biofilms. The formation of this complex community on biotic or abiotic surfaces facilitates cell adhesion to the host, the expression of virulence genes including resistance to antimicrobial agents and the formation of extracellular matrix that also contributes to resistance to antimicrobial agents (TSANG, BANDARA and FONG, 2012; NAVES et al., 2013; CHANDRA and MUKHERJEE, 2015).

Once established, biofilms of *Candida* spp. are reservoirs of persistent infections and are highly resistant to antifungal agents compared to planktonic cells (NOBILE and MITCHELL, 2006; CHANDRA et al., 2001; SAMARANAYAKE et al., 2005). It is estimated that approximately 80% of infections caused by *Candida* spp. are associated with the presence of biofilms (TSANG, BANDARA and FONG, 2012).

The formation of biofilms by *Candida* species occurs in three subsequent phases: the initial phase of adhesion of fungal cells to the substrate; Intermediary phase of polysaccharide extracellular matrix synthesis; and the maturation phase, to which the fungal cells are completely surrounded by this extracellular matrix (CHANDRA et al., 2001).

The components of the extracellular matrix differentiate according to the microorganisms present (DRENKARD, 2003). The extracellular matrix synthesized on biofilm, provides a highly hydrated environment to the cells of microorganisms present in the site (FLEMMING et al., 2000), and, the microcolonies are involved by the matrix and separated by water channels that provide the circulation of nutrients for the biofilm (DONLAN and CONSTERTON, 2002).

During the process of biofilm formation, the cells communicate by quorum sensing, modulating the development and growth of the same (HOGAN, 2006). Tirosol and farnesol are signaling molecules that were found in the biofilm of *Candida* spp. The tyrosol molecule promotes the formation of hyphae in the initial stage of biofilm formation, while farnesol inhibits the formation of hyphae avoiding the excessive biofilm growth (HOGAN, 2006; HORNBY et al., 2001). In addition, bacteria are often found in biofilms of *Candida* spp. indicating that such biofilms structures share properties with bacterial biofilms (DOUGLAS, 2003, DONLAN and CONSTERTON, 2002).

Resistance to antimicrobial treatment

Among the principal treatments to the world public health, the resistance of microorganisms to available medicines is currently considered one of the greatest challenges in the clinical area. The resistance consists in the ability of microorganisms to utilize intrinsic and extrinsic mechanisms that render treatment ineffective (SPRENGER and FUKUDA, 2016). Intrinsic resistance is characterized as natural resistance, being part of the phenotypic characteristics of the microorganism and all members of this species have this characteristic (FERNANDEZ and HANCOCK, 2012). Already the acquired resistance occurs when the species does not possess these characteristics by heredity, but can acquire resistance through spontaneous genetic alterations or horizontal transfer of genes (BRAUNER et al., 2016).

The development of resistance results from the survival of the microorganisms to the excessive use of the drug, as well as inadequate prescription of the drug, providing ideal conditions for the selection of resistant microorganisms and resulting in a treatment of refractory response (SANTAJIT and INDRAWATTANA, 2016).

Resistance to antifungals has resulted in a dramatic increase in the incidence of opportunistic and systemic fungal infections. Yeasts of the genus *Candida* have been described in the literature because they are resistant to several antifungal drugs such as *Candida albicans* and *Candida dubliniensis* that express the MDR1 gene associated with fluconazole resistance (JABRA-RIZK, FALKLER and MEILLER, 2004).

To treatment of *Candida* spp. infections, fluconazole (azoles class) is the antifungal most widely used. However, its efficacy is increasingly compromised especially in patients with AIDS, since the prolonged use of this antifungal leads to resistance (SANGLARD, 2003). Due to this increased of the use of azole, along with fungistatic drugs, probably resulted in the emergence of resistance of this class of antifungals.

Ramesh and coworkers (2010) related in a study using strains of *Candida* spp. isolated from infections in HIV-positive patients that the same showed resistance to the fluconazole, itraconazole and nystatin. Studies have also shown natural resistance of *Candida glabrata* and *Candida Krusei* species to fluconazole (SINGH-BABAK et al., 2012).

Beside fluconazole, other classes of antifungal agents are used in the treatment of *Candida* spp. infections such as polyenics (nistatin and amphotericin B), azoles (miconazole, itraconazole, voriconazole, posaconazole, ketoconazole) and echinocandins (caspofungin, micafungin and anidulafungin). However, despite the large diversity of accessible antifungals, the literature cites that many of these drugs are effective in fighting some infections caused by *Candida* spp. (RODRIGUES et al., 2014; MAUBON et al., 2014).

Bioactivity of isolated compounds by *Mentha* spp

The genus *Mentha* of the Lamiaceae family include approximately 30 plant species (LORENZI and MATOS, 2002) that produce essential oil with biocomponents such as menthol, menthone, isomenthone, 1,8 cineole (eucalyptol), methyl acetate, menthofuran, limonene, β-myrcene that some of it are of great importance in the pharmaceutical industry and medical industries (DESCHAMPS et al., 2008; GRULOVA et al., 2015; LORENZI and MATOS, 2002).

For medicinal purposes, essential oils with biocomponents in their composition are widely used to the treatment of digestive disorders, used as antispasmodic, antiseptic and anti-inflammatory (FEPAGRO, 2011) and due to the growth of cases of resistance to conventional drugs. These natural products have been the subject of studies demonstrating antibacterial, antifungal and antiviral potential (SAHARKHIZ et al., 2012; MIMICA - DUKI´C et al., 2003; ISCAN et al., 2002; SINGH, SHUSHNI and BELKHEIR 2011; MELZER et al., 2004). This activity can be explained by the fact that these substances called terpenoids have low molecular charge and easy penetration into cells (LORENZI and MATOS, 2002). In these circumstances, they can interact with the cell membrane of the microorganisms destabilizing them and favouring cell death (SCHELZ, MOLNAR and HOHMANN 2006; MKADDEM et al., 2009; ZORE et al., 2011).

Anti-Candida activity of the isolated compounds

Tests with pulegone showed antifungal activity against *Candida albicans* in diffusion method in plates with solid medium (ARRUDA et al., 2006). Aggarwal and coworkers (2002) observed that carvone inhibited the growth of two strains of *Candida albicans* in disk diffusion assay.

According to Raut and coworkers (2013), some terpenoids inhibit the formation of hyphae and, given their ability to damage the cell membrane, can be used in the control of this virulence factor, avoiding that the fungus promotes tissue invasion. In tests, Mcgeady, Wanley and Logan (2002) observed that in lower concentrations (sub-minimun inhibitory concentrations), carvone inhibited the growh of the filamentous tubes by *Candida albicans.* These filamentous tubes are important for the *Candida* spp. infection process, since these structures are associated with invasion of the fungus into host tissue.

Samber and coworkers (2015) reported that carvone and menthone showed antifungal activity against *Candida albicans*, *Candida glabrata* and *Candida tropicalis*. Also, in the same study it was observed that when incubated with the strains, these compounds inhibited in 100% ergosterol biosynthesis, the main component of the fungal cell membrane responsible by integrity and maintenance of the fungal cell function. Tests with carvone, menthone and pulegone showed effective antimicrobial action by the compounds against *Candida albicans* and *Candida glabrata* by microdilution technique and pulegone was the compound that showed greater activity (OUMZIL et al., 2002).

The anti-*Candida* activity of the isolated compound menthofuran is not well described, however, Saharkhiz and coworkers (2012) demonstrated antifungal activity in planktonic cells of *Candida albicans*, *Candida dubliniensis*, *Candida glabrata*, *Candida tropicalis*, *Candida krusei*, *Candida parapsilosis* and inhibition of the biofilm formation of *Candida albicans* and *Candida dubliniensis* by *Mentha piperita* essential oil containing menthofuran as constituent. In addition, studies developed in our laboratory observed the inhibition of growth of 19 planktonic cell strains, inhibition of biofilm formation and biofilm maturation in *Candida albicans* MYA-2876 by menthofuran (BONI et al., 2016).

Therefore, due to the dissemination of resistant microorganisms to conventional drugs (LEWIS, 2013) added the discovery to the antifungal potential of isolated compounds from *Mentha* spp., results in Beneficial effect to public health, since this new antifungal agent can replace or act as adjuvants to treatments already used once Candida species have demonstrated resistance to conventional drugs.

Conclusion

It has been observed in the literature that the increase of candidosis is becoming increasingly frequent, making the treatment of such infections difficult due to the susceptibility of *Candida* spp. to some antifungals. Various *Candida* species, especially *Candida albicans*, have been identified as relevant pathogens in hospital environments and the failure in the treatment against these microorganisms may result in the mortality mainly in immunosuppressed patients. Due to the clinical importance, is necessary alternative strategies to control these pathogens developing antifungal agents that alone or in combination may act in combat against these microorganisms. In this sense, the literature has been demonstrated promising results with biocomponents present in plants, specially antifungals including the essential oil of *Mentha* spp. against yeasts of the genus *Candida* becoming a new alternative source for the development of a new antifungal agents to fungal infections.

Acknowledgment

The authors are thankful to FAPESP and CNPq for their support.

References

AGGARWAL, K. K.; KHANUJA, S. P. S.; AHMAD, A.; SANTHA KUMAR, T. R.; GUPTA, V.K.; KUMAR, S. Antimicrobial activity profiles of the two enantiomers of limonene and carvone isolated from the oils of *Mentha spicata* and *Anethum sowa*. Wiley. *Flavour and Fragrance Journal*. v. 17. n. 1. p. 59– 63. USA, 2002. ISSN 1099-1026. [CrossRef]

ASMUNDSDÓTTIR, L. R.; ERLENDSDÓTTIR, H.; AGNARSSON, B. A.; GOTTFREDSSON, M. The importance of strain variation in virulence of *Candida dubliniensis* and *Candida albicans*: results of a blinded histopathological study of invasive candidiasis. Elsevier. *Clinical Microbiology and Infection*. v. 15. n. 6. p. 576–85. USA, 2009. ISSN 1198-743X. [CrossRef] [PubMed]

ARRUDA, A. T.; ROSSANA, M. P.; ANTUNES, R. M. P.; CATÃO, R. M. R.; LIMA, E. O.; SOUSA, D. P.; NUNES, X. P.; PEREIRA, M. S. V.; BARBOSA-FILHO, J. M.; CUNHA, E. V. L. Preliminary study of the antimicrobial activity of *Mentha x villosa* Hudson essential oil, rotundifolone and its analogues. SciElo. *Revista Brasileira de Farmacognosia*. v.16. n. 3. p. 307-311. João Pessoa, 2006. ISSN 1981-528X. [CrossRef]

BERMAN, J.; SUDBERY, P. E.*Candida albicans*: a molecular revolution built on lessons from budding yeast. *Nature Reviews Genetics*. v. 3. p. 918-30. USA, 2002. ISSN 1471-0064 [CrossRef] [PubMed]

BONI, G. C.; BUSATO, S. N.; SANTANA, P. L.; ANIBAL, P. C.; BORIOLLO, M. F. G.; BUSO-RAMOS, M. M.; BARBOSA, J. P.; OLIVEIRA, T. R.; HÖFLING, J. F. Antifungal and cytotoxic activity of purified biocomponents as carvone, menthone, menthofuran and pulegone from *Mentha* spp. *African Journal of Plant Science*. v. 10. p. 203-210. USA, 2016. ISSN 1996-0824. [CrossRef]

BRAUNER, A.; FRIDMAN, O.; GEFEN, O.; BALABAN, N. Q. Distinguishing between resistance, tolerance and persistence to antibiotic treatment. *Nature Reviews Microbiology*. v. 14. p. 320-330. USA, 2016. ISSN 1740-1534. [CrossRef] [PubMed]

BROWN, A. J. Morphogenetic signaling pathways in *Candida albicans*. In: CALDERONE R. A. *Candida* and candidiasis. Washington, DC: ASM Press. 95-106. 2002.

CALDERONE, R. A.; FONZI, W. A. Virulence factors of Candida albicans. *Trends in Microbiology*. v. 9. n. 7. p. 327-335. USA, 2001. PMID: 11435107. ISSN: 0966-842X. [CrossRef] [PubMed]

CHANDRA, J.; MUKHERJEE, P. K. *Candida* biofilms: Development, architecture and resistance. Microbiology Spectrum. v. 3. n. 4. USA, 2015. ISSN 2165-0497. [CrossRef] [PubMed]

CHANDRA, J.; KUHN, D.M.; MUKHERJEE, P. K.; HOYER, L. L.; MCCORMICK, T.; GHANNOUM, M. A. Biofilm formation by the fungal pathogen *Candida albicans*: development, architecture, and drug resistance. *Journal of Bacteriology*. v. 183. n. 18. p. 5385-5394. USA, 2001. PMID: 11514524. ISSN 1098-5530. [CrossRef] [PubMed]

CONSOLARO, M. E. L.; ALBERTONI, T. A.; SVIDZINSKI, A. E.; PERALTA, R. M.; SVIDZINSKI, T. I.E. Vulvovaginal candidiasis is associated with the production of germ tubes by *Candida albicans*. Springer. *Mycopathologia*. v. 159. p. 501–507. USA. 2005. ISSN 1573-0832. [CrossRef]

DAVEY, M. E.; COSTERTON, J. W. Molecular genetics analyses of biofilm formation in oral isolates. Wiley. *Periodontology*. v. 42. p. 13-26. USA, 2006. ISSN 1600-051X [CrossRef] [PubMed]

DESCHAMPS, C.; ZANATTA, J. L.; BIZZO, H. R.; OLIVEIRA, M. C.; ROSWALKA, L. C. Seasonal evaluation of essential oil yield of mint species. SciElo. *Ciência e Agrotecnologia*. v. 32. n. 3. p. 725–30. Lavras, 2008. ISSN: 1981-1829 [CrossRef]

DONLAN, R.M.; COSTERTON, J.W. Biofilms: survival mechanisms of clinically relevant microorganisms. *Clinical Microbiology Reviews*. v. 15. p. 167-93. USA, 2002. PMID: 11932229. ISSN 1098-6618. [CrossRef] [PubMed]

DOUGLAS, L.J. *Candida* biofilms and their role in infection. *Trends in Microbiology*. v. 11. p. 30-6.2003. PMID: 12526852. ISSN 0966-842X. [CrossRef] [PubMed]

DRENKARD, E. Antimicrobial resistance of *Pseudomonas aeruginosa* biofilms. *Microbes and Infection*. v. 5. p. 1213-19. 2003. PMID: 14623017. ISSN 1286-4579. [CrossRef] [PubMed]

ELLEPOLA, A. N. B.; SAMARANAYAKE, L.P. Adjunctive use of chlorexidine in oral candidoses: a review. *Oral Diseases*. v. 7. p. 11-17. 2001. PMID:11354914. ISSN 1601-0825. [CrossRef] [PubMed]

FEPAGRO. Circular Técnica. Espécies de Mentha com propriedades medicinais, aromáticas e condimentares. Porto Alegre. 2011. ISSN 0104-9097.

FERNANDEZ, L.; HANCOCK, R. Adaptive and mutational resistance: role of porins and efflux pumps in drug resistance. *Clinical Microbiology Reviews*. v. 25. p. 661–681. 2012. ISSN 1098-6618. [CrossRef] [PubMed]

FLEMMING, H. C.; WINGENDER, J.; MAYER, C.; KORSTGENS, V.; BORCHARD, W.; Cohesiveness in biofilm matrix polymers. In: ALLISON, D. G.; GILBERT, P.; LAPPIN-SCOTT, H. M.; WILSON, M. Community structure and co-operation in biofilms. Cambridge: Cambridge University Press. 87-105. 2000. [CrossRef]

GOW, N. A.; HUBE, B. Importance of the *Candida albicans* cell wall during commensalism and infection. *Current Opinion in Microbiology*. v. 15. n. 4. p. 406-12. 2012. ISSN 1369-5274. [CrossRef] [PubMed]

GRULOVA, D.; DE MARTINO, L.; MANCINI, E.; SALAMON, I.; DE FEO, V. Seasonal variability of the main components in essential oil of *Mentha × piperita* L. Wiley. *Journal of the Science of Food and Agriculture*. v. 95. n. 3. p. 621–7. USA, 2015. ISSN 1097-0010. [CrossRef] [PubMed]

HOGAN, D.A.; SUNDSTRON, P. The Ras/cAMP/PKA signailing pathway and virulence in *Candida albicans*. *Future Microbiology*. v. 4. n. 10. p. 1263-1270. London, 2009. ISSN 1746-0921 [CrossRef] [PubMed]

HOGAN, D.A. Talking to themselves: autoregulation and quorum sensing in fungi. *Eukaryotic Cell*. v. 5. n. 4. p. 613-619. 2006. ISSN 1535-9786. [CrossRef] [PubMed]

HORNBY, J. M.; JENSEN, E. C.; LISEC, A. D.; TASTO, J. J.; JAHNKE, B.; SHOEMAKER, R.; DUSSAULT, P.; NICKERSON, K. W. Quorum sensing in the dimorphic fungus *Candida albicans* is mediated by farnesol. *Applied and Environmental Microbiology*. v. 67. n. 7. p. 2982-2992. USA. 2001. ISSN 1098-5336. [CrossRef] [PubMed]

ISCAN, G.; KIRIMER, N.; KURKCUOGLU, M.; BASER, K. H.; DEMIRCI, F. Antimicrobial screening of *Mentha piperita* essential oils. ACS. *Journal of the Science of Food and Agriculture*. v. 50. p. 3943-3946. USA, 2002. PMID: 12083863. ISSN 1520-5118. [CrossRef] [PubMed]

JABRA-RIZK, M. A.; FALKLER, W. A.; MEILLER, T. F. Fungal biofilms and drug resistance. *Emerging Infectious Diseases Journal*. v. 10. n. 1. p. 14-19. 2004. ISSN 1080-6059. [CrossRef] [PubMed]

JACOBSEN, I.D.; WILSON, D.; WÄCHTLER, B.; BRUNKE, S.; NAGLIK, J.R.; HUBE, B. *Candida albicans* dimorphism as a therapeutic target. Expert Review and Anti-Infective Therapy. v. 10. n. 1. p. 85– 93. USA. 2012. ISSN 1744-8336. [CrossRef] [PubMed]

JALILZADEH, A.; MAHAM, M. Antidiarrheal activity and acute oral toxicity of *Mentha longifolia* L. essential oil. *Avicenna Journal of Phytomedicine*. v. 5. n. 2. p. 128-137. USA, 2015. PMID: 25949954. ISSN 2228-7930. [CrossRef] [PubMed]

LEWIS, K. Platforms for antibiotic discovery. Nature Reviews Drug Discovery. v. 12. n. 5. p. 371-387. USA, 2013. ISSN 1471-0064. [CrossRef] [PubMed]

LORENZI, H.; MATTOS, F. J. A. *Plantas Medicinais no Brasil - Nativas e Exóticas*. 2ª ed. Plantarum. Brasil. 2002. ISBN: 85-86714-28-3.

MAUBON, D.; GARNAUD, C.; CALANDRA, T.; SANGLARD, D.; CORNET, M. Resistance of *Candida* spp. to antifungal drugs in the ICU: where are we now? Springer. *Intensive Care Medicine*. v. 40. n. 9. p. 1241–1255. USA, 2014. ISSN 1432-1238. [CrossRef] [PubMed]

MAYER, F.L.; WILSON, D.; HUBE, B. *Candida albicans* pathogenicity mechanisms.*Virulence,* 2ª ed., v.15. n. 4. p. 119-128. USA, 2013. ISSN 2150-5608. [CrossRef] [PubMed]

MCGEADY, P.; WANLEY, D. L.; LOGAN, D. A. Carvone and peillaldehyde interfere with the sérum-induced formation of filamentous structures in *Candida albicans* at substantially lower concentrations than those causing significant inhibition of growth. *Journal of Natural Products.* v. 65. n. 7. p. 953-955. USA, 2002. ISSN 1520-6025. [CrossRef] [PubMed]

MELZER, J.; ROSCH, W.; REICHLING, J.; BRIGMOLI, R.; SALLER, R. Meta-analysis: phytotherapy of functional dyspepsia with the herbal drug preparation STW 5 (Iberogast). Wiley. *Alimentary Pharmacology & Therapeutics*. v.20. p. 1270-1287. USA, 2004. ISSN 1365-2036. [CrossRef] [PubMed]

MIMICA-DUKI´C, N. M.; BOZIN, B.; SOKOVIC, M.; MATAVUKLJ, M. Antimicrobial and Antioxidant Activities of Three *Mentha* Species Essential Oils. Thieme. *Planta Medica*. v.69. n. 5. p. 413– 419. 2003. ISSN 1439-0221. [CrossRef] [PubMed]

MKADDEM, M.; BOUAJILA, J.; ENNAJAR, M.; LEBRIHI, A.; MATHIEU, F.; ROMDHANE, M. Chemical composition and antimicrobial and antioxidant activities of *Mentha* (*longifolia* L. and *viridis*) essential oils. Wiley. *Journal of Food Science*. v. 74. n. 7. p. 358–363. USA, 2009. ISSN 1750-3841. [CrossRef] [PubMed]

MIZIARA, I. D.; LIMA, A.S.; CORTINA, R. A. C. Candidíase oral e leucopsia pilosa como marcadores de progressão da infecção pelo HIV em pacientes brasileiros. SciElo. *Revista Brasileira de Otorrinolaringologia*. v. 70. n. 3. p. 310-314. São Paulo, 2004. ISSN 0034-7299. [CrossRef]

MONTERO, J. G.; MARTÍN, A. D.; PIAPPÓN, M. R. P.; GARCIA-CABRERA, E. Infección fúngica invasiva em los pacientes ingresados em las áreas de críticos. Elsevier. *Enfermedades Infecciosas y Microbiologia Clínica*. v. 30. n. 6. p. 338-343. USA, 2012. ISSN 0213-005X. [CrossRef]

MORAIS, L. A. S. Influência dos fatores abióticos na composição química dos óleos essenciais. *Horticultura Brasileira*. v. 27. p.50-63. 2009. ISSN S0102-0536.

NAGLIK, J. R.; CHALLACOMBE, S. J.; HUBE, B. *Candida albicans* secreted aspartyl proteinases in virulence and pathogenesis. *Microbiolology and Molecular Biology Reviews*. v. 67. n. 3. p. 400-428. USA, 2003. PMID:12966142. ISSN 1098-5557. [CrossRef] [PubMed]

NAVES, P. L. F.; SANTANA, D.P.; RIBEIRO, E.L.; MENEZES, A.C.S. Novas abordagens sobre os fatores de virulência de *Candida albicans*. UFBA. *Revista de Ciências Médicas e Biológicas.* v. 12. n. 2. Salvador, 2013. ISSN 2236-5222. [CrossRef]

NOBILE, C. J.; MITCHELL, A.P. Genetics and genomics of *Candida albicans* biofilm formation. Wiley. *Cellular Microbiology*. v. 8, n. 9. p. 1382-1391. USA, 2006. ISSN 1462-5822 [CrossRef] [PubMed]

OUMZIL, H.; GHOULAMI, S.; RHAJAOUI, M.; ILIDRISSI, A.; FKIH-TETOUANI, S.; FAID, M.; BENJOUAD, A. Antibacterial and antifungal activity of essencial oils of *Mentha suaveolens*. Wiley. *Phytoterapy Research*. v. 16. p. 727-31. USA, 2002. ISSN 1099-1573. [CrossRef] [PubMed]

RAMESH, N.; PRIYADHARSINI, M.; SUMATHI, C.S.; BALASUBRAMANIAN, V.; HEMAPRIYA, J.; KANNAN, R. Virulence Factors and Anti-Fungal Sensitivity Pattern of *Candida* sp. Isolated from HIV and TB Patients. Springer. *Indian Journal of Microbiology*. v. 51. n. 3. p. 273–278. Indian, 2010. ISSN 0973-7715. [CrossRef] [PubMed]

RAUT, J.; SHINDE, R. B.; CHAUHAN, N. M.; KARUPPAYIL, S. M. Terpenoids of plant origin inhibith morphogenesis, adhesion, and biofilm formation by *Candida species*. *Biofouling*. USA, 2013; 29(1):87-96. ISSN 0892-7014. [CrossRef] [PubMed]

RODRIGUES, M. E.; SILVA, S.; AZEREDO, J.; HENRIQUES, M. Novel strategies to fight *Candida* species infection. *Critical Reviews in Microbiology*. v. 10. p. 1-13. USA, 2014. ISSN 0045-6454. [CrossRef] [PubMed]

SAHARKHIZ, M.J.; MOTAMEDI, M.; ZOMORODIAN, K.; PAKSHIR, K.; MIRI, R.; HEMYARI, K. Chemical Composition, Antifungal and Antibiofilm Activities of the Essential Oil of *Mentha piperita* L. *ISRN Pharmaceutics*. p. 1-6. New York. 2012. ISSN 2090-6153. [CrossRef] [PubMed]

SAMARANAYAKE, Y. H.; YE, J.; YAU, J. Y. Y.; CHEUNG, B. P. K.; SAMARANAYAKE, L. P. In Vitro Method to Study Antifungal Perfusion in *Candida* Biofilms. *Journal of Clinical Microbiology*. v. 43. n. 2. p. 818–825. Washington, 2005. ISSN 1098-660X. [CrossRef] [PubMed]

SAMBER, N.; KHAN, A.; VARMA, A.; MANZOOR, N. Synergistic anti-candidal activity and mode of action of *Mentha piperita* essential oil and its major components. *Pharmaceutical Biology.* p. 1495-1504. USA, 2015. ISSN 1744-5116. [CrossRef] [PubMed]

SANGLARD, D. Resistance and tolerance mechanisms to antifungal drugs in fungal pathogens. Elsevier. *Mycologist.* v. 17. p. 74-78. USA. 2003. ISSN 0269-915X. [CrossRef]

SANTAJIT, S.; INDRAWATTANA, N. Mechanisms of antimicrobial resistance in ESKAPE pathogens. *Biomed Research International*. v. 2016. 2016. ISSN 1110-7243. [CrossRef] [PubMed]

SARDI, J. C. O.; DUQUE, C.; MARIANO, F. S.; PEIXOTO, I. T. A.; HÖFLING, J. F.; GONÇALVES, R. B. *Candida* spp. in periodontal disease: a brief review. J.Stage. *Journal of Oral Science*. v. 52. n. 2. p. 177-185. 2010. PMID: 20587940. ISSN 1880-4926. [CrossRef]

SCHELZ, Z.; MOLNAR, J.; HOHMANN, J. Antimicrobial and antiplasmid activities of essential oils. Elsevier. *Fitoterapia.* v. 77. p. 279–285. 2006. ISSN 0367-326X. [CrossRef] [PubMed]

SCHULZE, J.; SONNENBORN, U. Yeasts in the gut: from commensals to infections agents. *Deutsches Ärzteblatt International*. v. 106. n. 51. p. 837-841. Berlin, 2009. ISSN 1866-0452. [CrossRef] [PubMed]

SINGH-BABAK, S. D.; BABAK, T.; DIEZMANN, S.; HILL, J. A.; XIE, J. L.; CHEN, Y-L.; POUNTANEN, S. M.; RENNIE, R. P.; HEITMAN, J.; COWEN, L. E. Global analysis of the evolution and mechanism of echinocandin resistance in *Candida glabrata*. *PLoS Pathogens*. v. 8. n. 5. USA, 2012. ISSN 1553-7374. [CrossRef] [PubMed]

SINGH, R.; SHUSHNI, M. A. M.; BELKHEIR, A. Antibacterial and antioxidant activities of *Mentha piperita* L.. Elsevier. *Arabian Journal of Chemistry*. v. 8. n. 3. p. 322-328. USA, 2011. ISSN 1878-5352. [CrossRef]

SPRENGER, M.; FUKUDA, K. Antimicrobial Resistance. New mechanisms, new worries. *Science*. v. 351. p. 1253-1254. USA, 2016. ISSN 1095-9203. [CrossRef] [PubMed]

SUDBERY, P. E. Growth of *Candida albicans* hyphae. *Nature Reviews Microbiology*. v. 9. n. 10. p. 737–748. USA. 2011. ISSN 1740-1534. [CrossRef]

TSANG, P. W-K.; BANDARA, H. M. H. N.; FONG, W-P. Purpurin suppresses *Candida albicans* biofilm formation and hyphal development. PloS One. v. 7. n. 11. USA, 2012. ISSN 1932-6203. [CrossRef] [PubMed]

VEIGA JR, V. F.; PINTO, A. C. Plantas medicinais: cura segura? SBQ. *Química Nova*. v. 28. n. 3. p. 519-28. São Paulo, 2005. ISSN 1678-7064. [CrossRef]

VYLKOVA, S.; CARMAN, A. J.; DANHOF, H.A.; COLLETTE, JR.; ZHOU, H.; LORENZ, M. C. The fungal pathogen *Candida albicans* autoinduces hyphal morphogenesis by raising extracellular pH. *MBio*. v. 2. n. 3. USA, 2011. ISSN 2150-7511. [CrossRef] [PubMed]

WÄTCHLER, B.; CITIULO, F.; JABLONOWSKI, N.; FÖRSTER, S.; DALLE, F.; SCHALLER, M.; WILSON, D.; HUBE, B. *Candida albicans*-epithelial interactions: dissecting the roles of active penetration, induced endocytosis and host factors on the infection process. *PLoS One*. v. 7. n. 5. 2012. ISSN 1932-6203. [CrossRef] [PubMed]

WEEMS, J. J. *Candida parapsilosis*: epidemiology, pathogenicity, clinical manifestations, and antimicrobial susceptibility. *Clinical Infectious Diseases*. v. 14. p. 756-66. Oxford, 1992. ISSN 1537-6591. [CrosRef] [PubMed]

ZORDAN, R.; CORMACK, B. Adhesins in opportunistic fungal pathogens. In *Candida* and Candidiasis, 2ª ed. Calderone RA, Clancy CJ. ASM Press. 2012: 243-59. 2012.

ZORE, G. B.; THAKRE, A. D.; JADHAV, S.; KARUPPAYIL, S. M. Terpenoides inhibit *Candida albicans* growth by affecting membrane integrity and arrest of cell cycle. Elsevier. *Phytomedicine*. v. 18. p. 1181-1190. USA, 2011. ISSN 1618-095X. [CrossRef]

Conflito de interesses: O presente artigo não apresenta conflitos de interesse.
Histórico do artigo: Submissão: 15/03/2017 | Aceite: 24/05/2017 | Publicação: 22/09/2017
Como citar este artigo: BONI, G. C.; FEIRIA, S. N. B.; HÖFLING, J. F. Purified bioactive compounds from *Mentha* spp. oils as a source of Candidosis treatment. A brief review. *Revista Fitos*. v.11, n.1. p. 95-106. Rio de Janeiro. 2017. e-ISSN 2446.4775. Disponível em: <http://revistafitos.far.fiocruz.br/index.php/revista-fitos/article/view/516>. Acesso em: 11 maio 2017.
