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Review Article

Bioactive Compounds from *Mentha Spp.* As a Potential Antifungal against Species of *Candida*. A Review Article -

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ABSTRACT

Fungi of the genus *Candida*, have become more frequent as agents of fungal infections, particularly associated with immunocompromised patients. It has been reported in the literature an increasing occurrence of resistance of these microorganisms to antifungal drugs available for the treatment of these pathologies, such as polyenes and azoles agents, which has led researchers in this field to seek new alternatives for drugs that have action against these organisms. Medicinal plants have long been used in the treatment of diseases through their extracts, essential oils and their bioactive components which makes them great source of new drugs research. Essential oils extracted from plants of the genus *Mentha* spp. have demonstrated potential of antimicrobial action, especially antifungal activity against fungi of the genus *Candida*.

INTRODUCTION

The use of plants as a therapeutic resource in the treatment of diseases is known millennially by many civilizations, being transmitted from generation to generation and used until today. In recent years, there has been a great scientific advance involving studies around this subject, aiming to obtain new compounds with therapeutic properties. Ethnopharmacology, an area of science that studies the interaction between plants and Human, have helped scientific advances in this area by cataloging species of plants considered medicinal by several peoples, allowing the empirical nature of the use of plants to give space for scientific reasoning, through research aimed at proving the pharmacological effect of therapeutics [1,2,3].

Studies involving the use of medicinal plants and phytotherapeutic action have already contributed to the obtaition of several drugs used in traditional medicine, among them emetin, salicylin, vincristine, among others [4,1]. In Brazil, there is great importance of studies on medicinal plants, mainly for the valorization of their use, including by the Ministry of Health, with incentive programs with the basic health units of the country. In the dental area, the recognition of phytotherapy as an integrative and complementary practice to oral health (resolution CFO-082/2008) was a great step to regulate the performance of the dentist surgeon in an area not yet explored by professionals [5]. Studies have shown that some oils and extracts obtained through some aromatic plants are efficient in antimicrobial control, including those that colonize the oral cavity [6,7].

With the increasing development of drug resistance and the appearance of undesirable effects by antifungal agents, research by new antimicrobial components has been a concern of many researchers [8]. In the last decade, interest in natural products has increased, with medicinal plants being sources of bioactive compounds. These compounds have been isolated and subjected to detailed structural analyzes, and their mode of action and target known. Many plants used in folk medicine have been studied for their antimicrobial activities, as a source of new antifungal compounds with few side effects, with a great range of action and low cost [9]. The screening of antibacterial plant extracts represents a continuous effort to find new compounds with potential to act against multiresistant bacteria [10].

The discovery of drugs involving the diversity of natural products, combined with synthetic drug methodologies and including the manipulation of biosynthetic pathways, provides a solution for the scientific community focused on the discovery and development of drugs [11]. According to the World Health Organization, at least 80% of the population in developing countries rely on "folk medicine" for the solution of health problems, and 85% of this total use medicinal plants for the treatment of various diseases. This means, according to the United Nations, that around four billion people worldwide rely on herbal remedies [12].

In this context, one of the plants better known as medicinal is *Mentha spp*., popularly known as Mint or mint. This plant is one of the most cited in ethnobotanical and ethno-pharmacological studies and is of great economic interest due to the production of essential oil rich in menthol [13]. Studies already carried out with Mentha spp. showed antimicrobial activities related to some species of this genus. The most cited activities of the plant are: antiviral, antibacterial and antifungal [14-16]. The activity found in literature of greater interest has been the antifungal, activity due to the innumerable cases of candidosis reported in the last decades.

In recent years, cases of fungal infections have increased. According to studies, part of this phenomena is due to the incidence of increasing cases of immunosuppressive diseases, such as AIDS (Acquired Immunodeficiency Syndrome) and cancer, diseases that cause weakness of the patient's immune system and allows fungi of the genus *Candida spp*., considered as commensal, because it is in equilibrium in the organism of healthy people, becomes an opportunistic pathogen, and can lead the patient to death [17,18]. It is known that among the fungi of the genus *Candida*, the most common species are: *C. albicans, C. krusei, C. tropicalis, C. guilliermondii, C. parapsilosis* and *C. glabrata* [19,20].

Due to increased cases of fungal infections, many conventional antimicrobials have been used more frequently, allowing the selection of resistant microorganisms and becoming one of the major challenges in treating the disease [21-24]. Thus, one of the most promising goals involving the study of plants with medicinal potential is to find effective active principles in the discovery of new antimicrobial drugs.

LITERATURE REVIEW

Mentha spp.

Mentha spp., are plants belonging to the family Lamiaceaes, is an annual herb, 30 to 60 cm high [13]. The aerial parts of *Mentha* spp. contain structures named as glandular trichomes, which are present in the axial part of the leaf, responsible for the secretion of essential oil produced by the secondary metabolism of the plant [25].

Natural products used as phytotherapics from *Mentha* spp. oil, one of the most consumed essential oils, can lead to new treatment modalities, aiding in the recovery and maintenance of health. Several species of *Mentha* spp. have been the subject of studies on their metabolic differences, chemical compositions, antibacterial, antifungal and antiviral properties [22,26-28]. Among the antimicrobial actions, stands out the antifungal effect on the genus *Candida* [13,29,30], and in the biofilm of *C. albicans* [22,31]. Agarwal, et al. [32], tested essential oil of mint in order to evaluate the inhibitory effect against biofilm formation by *C. albicans*, which showed a reduction of 80.87 and 74.16% of the biofilm formation for the two oils, respectively [32].

According to Mkaddem et, al. [33], *Mentha spp*. is composed of approximately 89% of monoterpenes [33]. Its main chemical components are menthol, mentone, isomentone, pulegone, piperitenone, piperitenone oxide, carvone and linalol [22,34,35]. Among these compounds, menthol is the most cited target of antimicrobial studies, and according to Al-Bayati et al. (2009), menthol showed antimicrobial activity in vitro tests [36].

Mimica-Dukic et, al. [37], observed that *Mentha aquatica* oil was composed of 16.94% of menthofuran and 14.15% of 1,8-cineol, among other compounds; while *M. piperita* had 39.63% of menthol and 8.93% of mentone in its composition, among other substances [37]. They also observed that the essential oil of *M. aquatica* shows antimicrobial activity against *Escherchia coli*, *Salmonella typhi*, *Micrococcus flavus*, *S.* aureus, *Bacillus subtillis* and C *albicans*; while *M. piperita* essential oil demonstrated activity against *E. coli*, *S. typhi*, *S. enteritidis*, *Shigella sonei*, *Sarcina lutea*, *M. flavus*, *S. aureus*, *Staphylococcus epidermidis*, *Bacillus subtillis* and *C. albicans*.

Iscan et, al. [15], found antimicrobial activity *in vitro Mentha piperita* assays. In addition to the oil, menthol and mentone fractions were isolated from the plant, and the species of microorganisms tested showed greater sensitivity to menthol than to menthona [15]. In another study, the oil of *M. piperita* showed high antifungal and inhibitory action on biofilm, and the main compound identified was menthol [22]. Yigit et, al. [38], showed that *Mentha piperita* possesses antimicrobial activity, with antifungal activity (*C. albicans*) and antibacterial activity (*E.coli*). The author highlights that one of the main responsible for the activity presented is menthol and pulegone [38].

Other studies have confirmed the excellent antimicrobial activity in essential oils rich in pulegone, reporting even greater susceptibility to *Candida* spp. To this compound specifically [35,39]. Mkaddem et, al. [33], demonstrated good antimicrobial activity of the essential oil of *Mentha longifolia*, whose major component was pulegone, showing strong activity against mycelial fungi and yeasts [33]. Oumzil et, al. [26], in tests performed with compounds of *Mentha suaveolens*, showed that all the compounds present antimicrobial activity. The highest sensitivity according to MIC (minimum inhibitory concentration) was in response to pulegone, menton, limonene and carvone respectively [26]. Carvone, a compound found in large amounts in the essential oil obtained from *M. suaveolens* in Egypt, appears to be involved with potent anti-candida according El-Kasshoury et, al. [40].

Through gas chromatography analyzes, Sarer et, al. [41], identified 37 compounds present in the essential oil of *M. spicata*, representing 95.3% of the oil, being the principal compounds the oxygenated monoterpenes (77.5%), with the presence of carvone (48.4%), and 1,8-cineol (21.3%) in greater abundance. They also found antimicrobial activity of essential oil against *S. aureus, Enterococcus faecalis, Pseudomonas aeruginosa*, *E. coli, C. albicans and C. tropicalis* [41].

Boni et, al. [42], worked with compounds isolated from *Mentha* (carvone, mentone, menthofuran and pulegone), finding antifungal activity at concentrations ranging from 0.5 to 8 mg / mL against strains of *Candida spp*., besides inhibiting adhesion, progression and formation of *C. albicans* MYA-2876 biofilm, and inhibition of germ tube formation [42]. Feiria et, al. [43], observed that the essential oils of *M. aquatica, M. arvensis and M. piperita* inhibited the formation of the mature biofilm of *C. albicans* MYA-2876 [43].

Candida spp. and Candidoses

Fungal infections caused by yeasts of the genus *Candida spp*., also called candidoses, are the most frequent infections associated with depletion of the immune system. The predisposing factors for the disease are: advanced age, hormonal diseases, nutritional deficiency, HIV incidence, frequent exposure to antimicrobials, chemotherapeutic treatments, carbohydrate-rich diets, use of prostheses and low immunity [18-20,44,45].

The yeast *Candida albicans* is the most frequent etiological agent in cases of fungal infections, being associated in up to 50% of cases of this type of disease [19,46]. This genus has the capacity to adapt and proliferate easily in the environment of the human body, in several places. This ability to adapt to different tissues of the human organism is related to its morphological transition capacity, called polymorphism, that presents variations of yeast growth for fungi forming hyphae [47]. According to Mayer et, al. [48], both the hyphal form and the yeast form are involved in the infection process [48], and the yeast, being smaller, is capable of spreading, whereas the hyphae invades the host tissue by penetrating the epithelium with the aspartyl proteinases and phospholipases, escaping from phagocytic cells [49-51].

The Secreted Aspartyl Proteinase (SAP) protein from the aspartic protease family consists of 10 individual members, Sap1 through Sap10, and has been described as the key to determining the virulence of C. albicans. Extensive research on Sap1 to Sap6 has demonstrated functional association of Saps with pathogenicity of *C. albicans*, by hydrolyzing host proteins, assisting in colonization and infection in different tissues. Sap proteins have several functions, ranging from tissue invasion to immune system evasion [52,53]. The presence of the SAP family gene is unique to pathogenic *Candida* species such as *C. albicans* [54], *C. dubliniensis* [55], *C. tropicalis* [56] e *C. parapsilosis* [57], but it is absent in non-pathogenic yeasts such as *Saccharomyces cerevisiae*, that increases the hypothesis that proteinases may be involved with virulence factors [58].

The advantage of having a family of proteinases such as Sap is that the production of several isoenzymes, each having a different optimal pH to perform its functions, can aid the colonization and infection of *Candida albicans* in different tissues and environments, since Sap has activity between pH 2-7, as Sap1-3 (associated with the yeast form) has pH optimum between pH 3-5, and Sap4-6 (associated with hyphae form) develops best at pH 5-7 [52].

Another advantage is in the breakdown of peptides. For example, Sap1, Sap2, Sap3 and Sap6 break peptide bonds between hydrophobic chains of amino acids, with Sap1, Sap2 and Sap6 breaking phenylalanine, whereas Sap3 breaks leucine [59]. The Sap2 enzyme degrades many human proteins in the mucosa, including extracellular matrix and surface proteins, such as keratin, collagen, fibronectin, laminin and mucin [58].

Another factor associated with virulence is the ability of *Candida* spp. to form biofilms, promoting the cellular adhesion and formation of the extracellular matrix of the biofilm, as well as the synthesis of proteins that favor its adhesion. The biofilm formation is a relevant fact due to its ability to be more resistant to antimicrobial agents, due to the difficulty of penetration in the extracellular matrix, and the action of the immune system, besides allowing the increase of the gene expression of mechanisms of resistance to antifungals as the efflux pumps [60].

Resistance To Antimicrobials and Medicinal Plants

The resistance of organisms against antifungal drugs is rapidly becoming a major problem, especially when it comes to infections in immunocompromised patients. The major antifungal agents known to treat candidoses are polyenes (nystatin and amphotericin B) and azoles (miconazole, fluconazole, ketoconazole) [20]. Despite the range of antifungal agents available for the control of these microorganisms, *Candida spp*. has developed molecular strategies for the expression of resistance to existing drugs. Results evidenced by Ramesh et al. (2010) showed that strains of *Candida spp*., from HIV patients shows resistance to fluconazol (23.5%), itraconazole (41.1%) and nystatin (11.9%), being that other species of *Candida* spp. showed resistance to almost all drugs tested, which makes it difficult to treat these infections [61]. *Candida* species have been reported as frequent agents in hospital infections of high resistance to antifungals [62,63]. Such evidence leads to an increasing need for the development of effective new drugs [62,64].

New approaches have been reported in the literature on the control of these microorganisms, such as the combined use of antifungal agents (synergism) and development of alternative compounds such as plant extracts, essential oils and derivatives isolated from plants [65]. The development of research on antimicrobial activity of plants for the production of new drugs aimed at reducing the side effects and resistance of microorganisms is a worldwide trend [66]. Despite the great diversity of existing antimicrobials, studies with medicinal plants aim to search for new drugs capable of presenting a greater spectrum of action, lower resistance index and lower toxicity [67,63]. In addition, the use of *Mentha* spp. has been associated with the development of new antimicrobial compounds, which will be of great importance as a result of the numerous reported cases of resistance to some drugs [68].

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