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Activity of phenolic compounds from plant origin against *Candida* species

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ABSTRACT

Candida albicans and other *Candida* species have been highly associated with several opportunistic fungal infections. Their ability to develop host infections is incited by different determinants, being virulence factors the most highlighted. Molecular targets of the antifungal drugs are crucial components for determination of yeast survival. Ergosterol, nucleic acids and glucan are the most studied molecular targets to destroy *Candida* species, being considered the basis of the development of new antifungal drugs. However, increasing levels of resistant *Candida* species to the current antifungal drugs have been observed, making ineffective those agents. Thus, other therapies more effective and safer than the current ones, are being studied, namely the use plant of extracts enriched in phenolic compounds. In this sense, this manuscript provides an historical perspective of the opportunistic fungal infections, molecular targets of the current anti-*Candida* drugs, as well as a general description of the active principles present in plants, focused on the antifungal potential of whole plant extracts and isolated phenolic compounds, against *Candida* species.

Contents

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1. Introduction

Fungi and other microbial species are widespread in the environment, including the soil, plants, trees, and even in the skin and other parts of the body. Most of them are not dangerous, even conferring some benefits to the host, being considered as commensal flora. Notwithstanding, some species in face to an abnormal overgrowth, might become harmful to the host and, in last instance, could compromise its life (Blanco and Garcia, 2008; Brunke and Hube, 2013).

In the last two decades, it has been observed a considerable increase in the incidence of deep fungal infections, not only in hospital environments, due to the increasing magnitude of organ transplantations, the rise of AIDS, the use of invasive devices (catheters, artificial joints and valves) and in immunocompromised patients, but also in the rest of population (Abi-Said et al., 1997; Eggimann et al., 2003a; Fanello et al., 2001; Kim and Sudbery, 2011; Li et al., 2006; Mayer et al., 2013; Raman et al., 2013; Silva et al., 2011a; Tsai et al., 2013; Wächtler et al., 2012). In parallel with this, and despite the advances on medical and chemical industries increased the life expectancy, due to the indiscriminate use of some chemical substances, it has been observed an increasing resistance of pathogenic microorganisms to conventional drugs, leading to development of other complications (Agarwal et al., 2010; Alves-Silva et al., 2013; Asgarpanah and Kazemivash, 2012; Asl and Hosseinzadeh, 2008; Bakkali et al., 2008; Kanafani and Perfect, 2008; Rana et al., 2011; Sher, 2009; Shojaii and Fard, 2012; Silva et al., 2011b; Singh et al., 2010).

Currently, fungal infections are the fourth leading causes of hematogenous infections and the most common involved fungi are *Candida* species, commensal microorganisms present in any healthy people (Pierce, 2005; Tsai et al., 2013). Symptoms and signals of fungal infections are not always visible, and an evolution to a systemic infection thrives very slowly, mostly of times, without any mistrust by the individual infected. There are several causal factors that contribute to those opportunistic fungal infections, some of them difficult, or even impossible, to avert. Pollution, smoking, certain drugs, poor diet, sedentary lifestyle and stress-inducing agents are some examples of aggressors (Devasagayam et al., 2004). However, not only external factors increase the organisms vulnerability to disorders, but also genetic changes in the cells, degeneration, reduction of the cells functionality (characteristic of aging process); damage in white blood cells and attacks in other cells of the organic defense system, weak the immune system, leading to a decrease in the ability to respond to invading organisms (Valko et al., 2007).

Natural defense systems are present in living organisms, but it is necessary to consider that in some conditions/situations, an external strengthening and complementation diets are essential (Carocho and Ferreira, 2013a; Devasagayam et al., 2004). It is an established fact that any unbalance affects the well-being of body and potentiates the growing and colonization of certain invaders, among other organic disorders. Thus, a balanced diet, containing all macro and micronutrients in right proportions is crucial to an optimal health, which was already stated by Hippocrates, the father of modern medicine, nearly 2.500 years ago: "*Let food be the medicine and medicine be the food*". There are some nutrients present in foods that can help to protect and strength the body, at greater or lesser degree (Devasagayam et al., 2004; Murray and Pizzorno, 1998; Singh et al., 2004; Valko et al., 2007).

Since the pre-historic era, plants, and other living organisms are used by primitive societies due to healing properties, being sought through botanical preparations. In fact, natural matrices, in particular, plants are extremely rich sources of natural biomolecules. Despite, with the passage of time, their use, as prevention or treatment of various conditions, became secondary and recently, plants have deserved a great relevance for scientific researchers that have been studying their bioactive properties; many of those properties have been related to their richness in phenolic compounds (Carocho and Ferreira, 2013a; Murray and Pizzorno, 1998; Wojdylo et al., 2007). Therefore, in the present manuscript, the activity of phenolic extracts and compounds against *Candida* species was revised and highlighted as an alternative to current antifungal drugs, which failed in treatment of several opportunistic fungal infections related with *Candida* species.

2. Opportunistic fungal infections

2.1. Historical perspective

Microorganisms are ubiquitous in the world, with a wide and fascinating variety and diversity. In the absence of microorganisms, the life on earth is not possible, with a close dependency on them. Otherwise, they are responsible for the onset of several diseases and disorders in the host (Amara and Shibl, 2013; Isolauri et al., 2002; Kaur et al., 2009).

In particular, yeasts, which belong to a category of fungi are part of the commensal flora of the healthy population. Colonization by some yeast species is beneficial to the host, because it not only limits the growth of other opportunistic pathogenic fungi, but also stimulates the functioning of the immune system. However, in face to an abnormal overgrowth, they are able to cause a wide variety of dysfunctions/disorders to the host. *Candida* species are a good example; although they are deemed a commensal microorganism, living smoothly in the inner warm creases and crevices of the gastrointestinal (GI) tract (and vaginal tract), they are able to cause problems, mainly vaginal infections (Asmundsdóttir et al., 2009; Brunke and Hube, 2013; Eggimann et al., 2003a; McCullough et al., 1996; Tsai et al., 2013).

During some days after birth, primarily, the mucosa of GI tract and upper respiratory passages are colonized by those species, as well as mouth, pharynx and larynx. Apart of the observed biochemical variations in the last trimester of pregnancy, namely progesterone, estradiol and glycogen levels, associated with an increase in vaginal pH, which favors the emergence of these infections (Carrara et al., 2010; Vázquez-González et al., 2013), other clinical status increase the vulnerability to yeast infections (diabetes, patient's submitted to broad-spectrum of antibiotic therapy, the use of oral contraceptives) (Epstein and Polsky, 1998; Geiger et al., 1995; Liu et al., 2009; Lott et al., 2005; Sobel, 2007; Tarry et al., 2005). Furthermore, and not least important, the increasing magnitude of organ transplantations, the rise of AIDS and the use of invasive devices (catheters, artificial joints and valves) are also major factors that contribute to higher patient's susceptibility to infections in hospitals (Epstein and Polsky, 1998; Kim and Sudbery, 2011; Pierce, 2005; Vázquez-González et al., 2013).

Seven *Candida* species are classified as having major medical importance, namely *Candida albicans Candida tropicalis*, *Candida glabrata*, *Candida parapsilosis*, *Candida stellatoidea*, *Candida krusei* and *Candida kyfer*, being *Candida albicans* the most important (Greenberg and Glick, 2003; McCullough et al., 1996; Silva et al., 2011a; Sullivan et al., 2004; Westwater et al., 2007).

Candidiasis, the most common opportunistic yeast infection in the world has been related in majority with *Candida albicans*. This microorganism is a causative agent of mouth and mucocutaneous infections, among others more complicated, such as septicemia, endocarditis, meningitis, and peritonitis, especially in patients with reduced immune function or taking antibiotic therapies (Brunke and Hube, 2013; Greenberg and Glick, 2003; McCullough et al., 1996). Nevertheless, in the last two decades, in face to the rapid increase in the incidence of opportunistic fungal infections, numerous studies had revealed that also other species of