

The chemical composition and inhibitory action of *Punica granatum* (L.) extracts against *Candida* spp.: A brief review

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ABSTRACT

Faced with increasing cases of antimicrobial resistance, new compounds from natural products have been scientifically investigated for their antibacterial and antifungal action. Ethnopharmacological studies have shown that many plants extracts have been a source of new bioactive compounds acting against several types of diseases, attracting attention to researchers, aimed at their application in medicine. Studies were carried out with extracts from *Punica granatum* L. and its compounds have showed antioxidant, and anti-inflammatory effects for the treatment of oral diseases, skin diseases, diarrhea, helminth infections, microbial infections and respiratory diseases among others. Its antimicrobial activity has been investigated recently, and may be present in various parts of the plant such as flowers, leaves, stems and bark. It was found high activity of the *P. granatum* methanolic extracts against strains of *Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus epidermidis*, *Enterococcus faecalis*, *Escherichia coli*, *Candida albicans* and other species. *Candida* yeast is an opportunistic pathogen and its virulence factors may contribute to its invasion and pathogenicity. These considerations served as a basis of the studies carried out in this review work, aiming to evaluate the use of extracts obtained from different parts of the *P. granatum* L. fruits as antimicrobial agents, associated to researches of components with bioactive potential present in these structures, determined by mass spectrometry.

Keywords: *Punica granatum*, extract, antifungal, *Candida* spp.

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INTRODUCTION

Despite the successive advances in the use of drugs in the treatment of various diseases, a large part of the world population still depends on traditional medicine based on phytotherapy (Azaizeh et al., 2003). Knowledge about the medicinal use of plants and their properties have been transmitted from generation to generation (Lev and Amar, 2000), and ethnobotany is a very important area of study and knowledge around the world. This science shows a healthy relationship between humans and nature establishes the possibility of finding new uses for medicinal plants and can be used to discover new medicinal products derived from plants (Heinrich, 2000). For centuries, the bark, leaves, flowers and fruits of *Punica granatum* L. (*Punicaceae*), popularly known as pomegranate, have been used to treat diseases

(Gracious Ross et al., 2001). Studies with extracts from *P. granatum* and compounds had shown antioxidant effects (Ricci et al., 2006), antiinflammatory (Lansky and Newman, 2007), hepatoprotective (Celik et al., 2009) for the treatment of oral diseases (Fengchun et al., 1997), skin, among others (Hu, 1997). It was also used to treat acidosis, dysentery, microbial infections, diarrhea, helminthes, hemorrhage and respiratory pathologies (Fuentes and Exposito, 1995).

The antimicrobial activity of *P. granatum* has been investigated (Vasconcelos et al., 2003; Pereira et al., 2006b), and may be present in some metabolic toxins or broad spectrum antibiotic compounds contained in the bark (Voravuthikunchai et al., 2004). Duraipandiyani et al. (2006) found high activity of the pomegranate with the

methanolic extract against the strains of *Bacillus subtilis*, *Staphylococcus aureus*, *S. epidermidis*, *Enterococcus faecalis*, *Escherichia coli* and *Candida albicans*. Braga et al. (2005) observed that the methanolic extract of the *P. granatum* fruits was able to inhibit not only the growth of *Staphylococcus aureus* FRI722, but also the production of enterotoxins. Höfling et al. (2010) found antifungal activity of pomegranate extracts against several species of *Candida* spp.

Candida yeast is an opportunistic pathogen and many virulence factors may contribute to its invasion and pathogenicity, as well as its ability to adhere to tissues, the conversion of its unicellular form to filamentous and expression of extracellular enzymes, such as aspartyl protease and phospholipases (Calderone and Fonzi, 2001).

Although *C. albicans* is the main isolated species of clinical specimens in AIDS patients, it is known that other non-*albicans* species such as *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. tropicalis* are highly prevalent in infections (Ruhnke, 2006). Candidiasis has re-emerged with a high mortality rate, with a prevalence of 45% in the groups of compromised patients (Wenzel and Gennings, 2005). Failure of the action of antifungals used in diseases caused by non-*albicans* species such as *C. glabrata* and *C. krusei* is now a therapeutic challenge. It is known that *C. krusei* infections are becoming prevalent due to the increase in the immunocompromised population, mainly with HIV (Human Immunodeficiency Virus) (Seneviratne et al., 2007), but it is also known that the resistance phenomenon of antimicrobial microorganisms is a fact to consider.

Microbial resistance is related to the loss of susceptibility of a microorganism to an antimicrobial agent which can be visualized by an *in vitro* susceptibility test in which the minimum inhibitory concentration is the lowest concentration of the drug which prevents visible growth of the microorganism (Alves et al., 1997; Marichal et al., 1999). Several antifungal drugs, such as fluconazole, ketoconazole, nystatin, amphotericin B, and 5-fluorocytosine, may interfere with certain virulence factors (Ellepola and Samaranayake, 1998; Hazen et al., 2000), but emerging drug resistant strains have impeded antifungal treatment, often restoring the patient's health (Odds et al., 2003).

Research aiming at increasing knowledge about the antimicrobial potential for plants, particularly *P. granatum*, or its pharmacological components, relating the effects of its pharmaceutical properties to its antimicrobial activity, may contribute to its acceptance as an alternative medicine or to the allopathic treatment as a whole.

LITERATURE REVIEW

Medicinal plants: *Punica granatum*

The pomegranate, *P. granatum* L., has long been known

for its edible fruit, being mentioned in the Bible and in the Alcoran, being associated with fertility. It is native to Persia and spread throughout Asia, North Africa and Mediterranean Europe, including Turkey. Pomegranate plantations in Turkey have grown rapidly in recent years, with production exceeding 100,000 tonnes in 2007 (Ozgen et al., 2008).

Pomegranate is known to be one of the healthiest fruits because of its high antioxidant activity (Gil et al., 2000; Aviram et al., 2008) and high content of anticarcinogenic compounds (Kim et al., 2002; Lansky et al., 2005; Malik et al., 2005; Adhami and Mukhtar, 2006; Malik and Mukhtar, 2006; Bell and Hawthorne, 2008). Folk medicine recommends both the stem and fruit peel to treat various diseases. The stem bark is used as a vermifuge, especially for tapeworms. From the fruit, dried or fresh peels are used for the treatment of diarrhea, skin and mucous infections and fresh seeds, with their pink and succulent wraps, for mouth and throat affections (Matos, 1989; Lansky et al., 1998).

Among the constituents present in the fruit of *P. granatum* L. are alkaloids (peletierina, methylpeletierina, pseudopeletierina and isopeletierina), manita, several phenols, ellagic acid and gallic acid. The peel of the pomegranate fruit contains alkaloids and approximately 20% of tannins, including punicalin, punicalagina, granatins A and B, galagildylactone, casuarinina, pedunculagine, telimagrandin I and corilagina, with antibiotic action (Fetrow and Avila, 2000). It is popularly used in the treatment of sore throats, hoarseness and inflammation of the mouth. From the pericarp, rich in tannins, granatins A and B, punicalagina and punicalin were isolated, being the main ones responsible for the antimicrobial activity (Catão et al., 2006).

Pomegranate is a rich source of phenolic compounds, which includes flavonoids and hydrolyzed tannins (Afaq et al., 2005). Extracts from different parts of the pomegranate fruit such as juice (Aviram et al., 2000), seeds (Singh et al., 2002; Wang et al., 2004) and bark (Singh et al., 2002; Lansky and Newman, 2007) have shown great antioxidant activity.

Monitoring the ethanolic extracts from *P. granatum* by mass spectrometry, Anibal et al. (2013) detected various compounds, among them delphinidin 3-O-glucoside, puniacortein A, puniacortein B, pedunculagin, tellimagrandin, glucose, citric acid, caffeic acid, punicic acid (*cis*-9, *trans*-11, *cis*-13 octadecatrienoic acid), ellagic acid, quercetin, delphinidin, gallagylidilacton and punicalagin from pericarp; and puniacortein A, puniacortein B, corilagin, glucose, citric acid, caffeic acid, punicic acid (*cis*-9, *trans*-11, *cis*-13 octadecatrienoic acid), pedunculagin, tellimagrandin and punicalagin from the peels.

Phenolic compounds properties of *P. granatum*

The polyphenolic compounds comprise a group of the

class of secondary plant metabolites, which act as antioxidants (Manach et al., 2005). Phenolic compounds are essential for plant growth and reproduction and are produced as a plant response to damage caused by pathogens. At low concentrations, they protect food from oxidative deterioration. At high concentrations, its oxidative product may interact with proteins, carbohydrates and minerals (Karakaya, 2004). Flavonoids made up one of the most numerous groups of phenolic compounds found in plants and fruits (Schinella et al., 2002; Tepe et al., 2005). Some of them are involved in the healing process of diseases caused by free radicals (Czinner et al., 2000). Many compounds of *Punica granatum*, such as alkaloids, flavonoids, polyphenols (such as delphinidin, cyanidin and pelargonidin) and hydrolyzable tannins, such as punicalin, pedunculagine, punicalagin, gallic acid and ellagic acid (glucose esters) have strong antioxidant properties and have been investigated (Du et al., 1975; Tzulker et al., 2007). Anthocyanins, belonging to the family of flavonoids biosynthesized from the phenylpropanoid pathway, constitute an important class of polyphenols (Saviranta et al., 2008). They are composed of mixed biosynthesis, involving blocks of the polyacetate pathway and the chiquimato pathway (Lobo and Lourenço, 2007). Duman et al. (2009) correlated that the large amount of anthocyanins presents in the pomegranate juice exerted high antibacterial and antifungal activity in the tests performed due to its antioxidant capacity. This class of compounds has demonstrated antioxidant, anti-inflammatory, anti-atherosclerotic and anticancer activities in several studies (Kong et al., 2003a; Zafra-Stone et al., 2007; Srivastava et al., 2007). The common form of aglycone, anthocyanidin, found is cyanidin, delphinidin, peonidine, petunidine, malvidin and pelargonidin. Chemical analyzes performed by Dudonné et al. (2009) showed that the phenolic compounds of pomegranate contain high levels of hydrolysable tannins, such as punicalina, punicalagina, pedunculagina and punigluconina.

The complexation between tannins and proteins is the basis for their properties as factors controlling insects, fungi and bacteria as well as for their pharmacological activities (Simões et al., 2007), and may act as inhibitors of reverse transcriptase and HIV (Kilkuskie et al., 1992).

In vitro tests performed with extracts rich in tannins or with pure tannins have identified several biological activities of this class of substances. Among these we can mention: bactericidal and fungicidal action (Scalbert, 1991; Chung et al., 1998c), antiviral (Okuda et al., 1993; De Bruyne et al., 1999b), inhibition of enzymes such as glycosyltransferases from *Streptococcus mutans* and *S. sobrinus* (Hattori et al., 1990; Ooshima et al., 1993), inhibition of lipid peroxidation and free radical scavenger (Hagerman et al., 1998; Moure et al., 2001) and antitumor action (Wang et al., 1999; Dufresne and Farnworth, 2001).

A number of bacteria are sensitive to tannins, among them *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Bacillus anthracis* and *Shigella dysenteriae*. There are three hypotheses for the mechanism of antimicrobial action. The first hypothesis assumes the inhibition of bacterial and fungal enzymes and/or the complexation of the substrates of these enzymes; the second would be the action of tannins on the cell membranes of microorganisms, modifying their metabolism. Finally, the third hypothesis mentions the complexation of tannins with metal ions (Mila et al., 1996), thus reducing the availability of these essential elements for the metabolism of microorganisms (Simões et al., 2007).

Elsherbiny et al. (2016) worked with the methanol extract of pomegranate peels demonstrating inhibition on mycelial growth of *Fusarium sambucinum* and a complete inhibition on spore germination using this extract. Twenty four individual phenolic compounds were identified and quantified in the extract using HPLC analysis, with the total phenol content as 104.6 mg GAE/g extract according to the Folin-Ciocalteu method.

Polyphenols are hydrolyzable phytochemicals and the more hydrophilic the extractive solvent the better those compounds will be recovered from the plant (Negi and Jayaprakasha, 2003; Alzoreky and Nakahara, 2003). The mechanism responsible for the toxicity of the phenolic compound against microorganisms may be in the reaction with the sulfhydryl groups and substrates of the microorganism, interfering with the bacterial protein secretion (Machado et al., 2003; Naz et al., 2007).

Yeasts of the genus *Candida*

Candida spp. are yeasts that normally present as individual cells and reproduce asexually by budding. *Candida albicans* is a polymorphic diploid yeast with eight pairs of chromosomes. It can replicate under anaerobic conditions, as in the intestine (Kruppa, 2008). Almost 200 species of *Candida* are known, but only a few are important to man. The most important are *C. albicans*, *C. glabrata*, *C. krusei*, *C. dubliniensis*, *C. tropicalis*, *C. parapsilosis*, *C. guilliermondii* and *C. lusitaniae* (Bernhardt and Knoke, 1997; Calderone, 2002; Hube, 2004).

Several factors, such as adhesion to host tissue, morphological characteristics, germ tube formation, contact perception, phenotypic change, synergism with bacteria, production of hydrolases or other metabolites, and production of extracellular enzymes were proposed as virulence factors of *C. albicans* (Odds, 1988; Olsen 1990; Bendel, 2003). Adherence of yeast to host mucosal surfaces is a prerequisite for colonization and infection (Olsen, 1990; Bendel, 2003). Mucous host surfaces serve as a reservoir for the spread of infections, such as gastrointestinal infection, especially in immune-

compromised patients (Nikawa et al., 2006). During the early stages of superficial mucosal infection, *C. albicans* forms filamentous hyphae (Sherwood et al., 1992; Gow et al., 1994), along with the release of various hydrolytic enzymes (Ruechel, 1990). Its hyphae have ability to penetrate into the host tissue, adhering to a much greater extent when compared to the cellular form. Thus, hyphae are an important instrument for the attack and the infectious process (Järvensivu et al., 2004). In the United States, yeast infection is classified as the fourth most common cause of nosocomial blood infection (Wisplinghoff et al., 2004). In Brazil, *Candida albicans*, *C. tropicalis* and *C. parapsilosis* are the most common species isolated from blood-to-colon infection in several medical centers (Colombo et al., 2006; Medrano et al., 2006; Passos et al., 2007).

Resistance to antifungal agents

The occurrence of systemic fungal infections has increased, along with the growing number of immunocompromised individuals whose population increases in parallel due to the AIDS pandemic, cancer chemotherapy treatment and organ transplantation. Among these populations, especially those infected with HIV, fluconazole doses are generally given prophylactically to prevent the occurrence of opportunistic fungal infections. Thus, prolonged treatments results from the appearance of *C. albicans* phenotypes resistant to azole antifungals (White et al., 1998; Kontoyiannis and Lewis, 2002). Oropharyngeal candidiasis along with antifungal cross-resistance is one of the major problems faced by HIV-positive patients (Vanden Bossche et al., 1994). Immunosuppressed patients are at high risk of infection with resistant organisms, as well as patients who had exposure to high doses of fluconazole (>10 g), or treatment with long duration (Maenza et al., 1996).

Several investigations suggest that resistance to fluconazole may be induced in patients who are under a prolonged period of treatment (Ruhnke et al., 2000).

The wide use of itraconazole and fluconazole is considered the main cause of resistance to azoles (Goldman et al., 2000). Invasive candidiasis is an important cause of complications and death in hospitalized patients. Amphotericin B has been used as standard treatment for five decades, but its toxic effects have limited its use (Rex et al., 1994). However, some species of *Candida*, such as *C. krusei* and *C. glabrata*, are frequently resistant to fluconazole. This fact and the fungistatic activity of triazoles constitute the main limitations of fluconazole as the first line in the therapy for candidemia. Increased prevalence of microbial resistance to commercial antifungal drugs has been observed. The low therapeutic efficacy observed in some infections may be due to the inefficient penetration of the drugs into the infected cells, not allowing the drug to reach the yeast

(Drago et al., 2000). All these aspects make the demand for new antimicrobial compounds important, including those that may be present in plant extracts (Filoche et al., 2005).

Extracts of *P. granatum* activity on *Candida* spp.

With the increasing development of drug resistance and the appearance of undesirable effects by antifungal agents, research on new antimicrobial components has been a concern of many researchers (Phongpaichit et al., 2005). Bioactive compounds have been isolated and subjected to detailed structural analyzes, and their mode of action and target known (Ishida et al., 2006). 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 to the scientific community focused on the discovery and development of drugs (Newman and Cragg, 2007).

When analyzed the extract from the pomegranate in the inhibition of yeasts of the genus *Candida*, several works show activity of this plant, as demonstrated by Navarro et al. (1996), Vasconcelos et al. (2003), Durairandiyan et al. (2006), Vasconcelos et al. (2006), Reddy et al. (2007), Al-Zoreky (2009) and Duman et al. (2009). Anibal (2007) evaluated the activity of the pomegranate through crude extracts dichloromethane and methanolic, against standard strains of *C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*, *C. dubliniensis*, *C. utilis*, *C. guilliermondii*, *C. lusitaniae*, and *C. rugosa*, demonstrating antifungal activity of this plant of interest for alternative therapy against these microorganisms.

Anibal et al. (2013) showed that ethanolic extracts obtained from pericarp and peel presented potential inhibitory activity, with a minimum inhibitory concentration of 125 µg/ml. These data indicate that the activity of *P. granatum* probably occurs in the compounds present in the pericarp and peel of this fruit. The samples of pericarp and peel extract, that presented better results against *Candida* species, had a high concentration of the punicalagin compound as a differential, in addition to other tannins, such as pedunculagin and tellimagrandin. Therefore, punicalagin and gallagylidilacton are apparently the major compounds involved in antifungal activity observed in the extracts of *P. granatum*.

Catão et al. (2006) and Fetrow and Avila (2000) indicated tannins, such as punicalin, punicalagin, gallagylidilacton, pedunculagin, tellimagrandin I and corilagin, to be responsible for the antimicrobial activity. Endo et al. (2010) observed elevated activity of the isolated compound punicalagin against *C. albicans* and *C. parapsilosis*, indicating this substance as a potent antifungal agent, without however, elucidating the mechanism of action. Vasconcelos et al. (2003) assigns

to the tannins, the ability to inhibit the growth of yeast *Candida* species due to their actions in the cell, specifically in the cell membrane, precipitating proteins.

DISCUSSION

The plant kingdom represents a large reservoir of pharmacologically active molecules to be discovered, and study containing many different secondary metabolites involving the active principle has become a promising field for the discovery of new phytomedicines as an alternative treatment of diseases (whether they are caused by bacteria or fungi). In the literature there are several studies showing, in particular, antimicrobial and antifungal effects on microorganisms of medical interest, as well as having a significant treatment in resistant strains and not causing such dangerous side effects for the health; justifying the researches with purposes of evaluating the antimicrobial potential of these phytotherapies. As can be seen in this review, pomegranate has antimicrobial compounds that make this plant a promising alternative for treatment of diseases.

Such plant has many kinds of properties and bio-components from its secondary metabolites, as alkaloids and polyphenolic compounds, involving antimicrobial properties. Several studies had been showed effects against many bacteria and yeasts, especially against *Candida* spp., that has increased the infections on groups of compromised patients with the increasing development of drug resistance and the appearance of undesirable effects by antifungal agents.

The discovery of drugs involving the diversity of natural products, combined with synthetic drug methodologies and the manipulation of biosynthetic pathways, provides an alternative solution to the scientific community focused on the discovery and development of drugs, making the pomegranate a potential plant alternative for treatment of diseases.

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