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 provide 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.

Keywords: Phytochemicals; Plant extracts; Phenolic compounds; Antifungal activity; *Candida* species

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 than 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 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 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 fungi are involved in some hospital infections, like *Aspergillus* spp., *Zygomyces* spp., *Fusarium* spp., *Scedosporium* spp., *Cryptococcus* spp., *Trichosporon* spp., *Geotrichum* spp., and *Rhodotorula* spp. (Kwamin et al., 2013; Martins et al., 2014; Tsai et al., 2013; Vázquez-González et al., 2013). But, *C. albicans* still counting nearly 50-90% of isolates from fungal infections, being able to cause serious hematogenous infections that, directly, affect the welfare of individuals (Vázquez-González et al., 2013).

2.2. Anti-Candida targets

Due to the high incidence of opportunistic fungal infections, namely triggered by *Candida* species, a wide variety of experimental studies have been carried out towards the discovery of effective treatments against these opportunistic and pathogenic microorganisms. Cellular morphology, physiology, and metabolism are crucial aspects in fungal cells survival.

All living organisms communicate with the surrounding environment and, in the case of *Candida* cells, the communication is established through the cellular membrane. Quorum-sensing is considered the mechanism of microbial communication, and for *C. albicans*, the main quorum sensing molecules are farnesol, tyrosol and dodecanol. This mechanism is not only incited by yeast growth but also by the hyphal formation (Lu et al., 2006; Mayer et al., 2013; Wyk et al., 2009). One of the main functions of cellular membrane is to maintain cells homeostasis to ensure the protection of internal organelles, being the first barrier in *Candida* cells. In the membrane, there are a wide variety of components present, playing different functions. The phospholipid bilayer is a

common membrane to all eukaryotic cells, as also proteins, carbohydrates, other lipids (i.e. sterols, fatty acids, glycerol and esters) and even association of those substances. In the case of fungal cells, such as *Candida* species, ergosterol is the specific and most abundant sterol. Those molecules play important roles in the maintenance of integrity and fluidity of the membrane, acting as secondary messenger in the signal development in order to warrant the proper cell function (i.e. growth, division and reproduction). Thus, ergosterol is considered the main target of antifungal drugs (Ghannoum and Rice, 1999; Kanafani and Perfect, 2008; White et al., 1998).

Chemical substances could act by three main different ways in *Candida* cells: in the ergosterol biosynthesis (i.e. azoles) (Ghannoum and Rice, 1999; Kanafani and Perfect, 2008; Lamb et al., 1999; Lupetti et al., 2002; Sanglard, 2002); interacting with ergosterol and intercalating between membrane (i.e. polyenes) (Ghannoum and Rice, 1999; Kanafani and Perfect, 2008; Kontoyiannis and Lewis, 2002); or even causing ergosterol depletion (i.e. allylamides) (Kanafani and Perfect, 2008; Kontoyiannis and Lewis, 2002; White et al., 1998).

Unfortunately, in the last years, it has been observed an increasing drug resistance to those classes of antifungal agents, being ineffective even in higher doses. Some virulence mechanisms have been studied, not only to explain the increasing rates of antifungal drugs resistance, but also to discover/create new and promising antifungal strategies. So far, the most frequent virulence mechanism associated with *Candida* species infections is the ability of adaptation to a wide variety of habitats, commonly known as morphological transition. Notwithstanding, other factors, as the ability for biofilm formation, the secretion of hydrolytic enzymes (such as proteases and phospholipases), and the expression of adhesins and invasins linked with the dimorphic

phases and phenotypic switching, have been associated with *Candida* species infections (Mayer et al., 2013; Tsai et al., 2013).

In this sense, different molecular targets needs to be studied as also more effective and selective compounds against the fungal cell wall; compounds to inhibit nucleic acids, to affect the plasma membrane, ergosterol, phospholipid, sphingolipid and protein biosynthesis; intermediates of the metabolism of nucleic acids and amino acids; compounds that affect efflux pumps, proton ATPases and other enzymes. The study of the fungal virulence factors and involved genes on antifungal resistance, among other important biological components with a direct interference on drug resistance, is crucial (Franz et al., 1998; Kanafani and Perfect, 2008; Lupetti et al., 2003; Mayer et al., 2013; Noël, 2012; Perlin, 2014; Sangamwar et al., 2008; Sanglard and Odds, 2002; White et al., 2002, 1998). Mayer et al. (2013) quoted polymorphism, secretion of hydrolases; pH sensing and regulation; metabolic adaptation; environmental stress response; heat shock proteins and small heat shock proteins, and metal acquisition as the most important virulence factors and fitness attributes, while Lewis et al. (2012) proposed that the inhibition of macrophage cell division or arrest of the host macrophages to confine the pathogens, is another virulence attribute of *Candida* species, in particular *C. albicans*.

2.3. Current anti-Candida drugs

Currently, there are five main classes of antifungal agents widely used at a medical level against the major fungal pathogens, including *Candida* species: polyenes, azoles, allylamines/thiocarbamates, fluoropyramidines and echinocandins (Maurya et al., 2013).

Azoles, polyenes and allylamine/thiocarbamates act, direct or indirectly, in the ergosterol present in all *Candida* species (Kontoyiannis and Lewis, 2002; Lupetti et al., 2003).

Polyenes comprise a class of antifungal agents that affect cellular membranes containing ergosterol. These agents present amphipathic properties which allow their intercalation between membranes containing ergosterol, forming channels that favor the ionic unbalance and destroy the proton gradient (Ghannoum and Rice, 1999). Nystatin and amphothericin-B are the most common used polyenes (Eggimann et al., 2003b). Nevertheless, not only primary but also secondary resistance of *Candida* species, namely *C. albicans, C. lusitanea, C. guilliermondii* and *C. glabrata*, have been observed (Ghannoum and Rice, 1999; Kontoyiannis and Lewis, 2002; White et al., 1998).

Azoles are another class of antifungal agents in which the target is over again ergosterol, but in this case affects its biosynthesis. Firstly introduced during the 1980s and used by oral administration, to treat oropharyngeal candidiasis in patients with VIH+, they act as inhibitors of sterol 14α-demethylation. The remotion of the C32-methyl group at a 14α- from precursor sterols, catalyzed by a microsomal cytochrome P450 monooxygenase, affect the main sterol present on fungal cells membranes: Erg11p, a lanosterol 14-alpha-demethylase. Miconazole and econazole were the original used azole compounds, followed by ketoconazole, fluconazole and itraconazole (Eggimann et al., 2003b; Ghannoum and Rice, 1999; Sardi et al., 2013). However, and despite during several years those drugs presented a great efficacy as antifungal agents, resulting in a widespread use, currently it is being observed an increasing emergence of *Candida* species-resistance (namely *C. albicans, C. glabrata, C. parapsilosis, C. krusei* and *C. lusitaniae*) (Develoux and Bretagne, 2005; Noël, 2012; Vázquez-González et al., 2013).

Allylamines (i.e. naftifine and terbinafine) and thiocarbamates (i.e. tolnaftate and tolciclate) are the third class of antifungal agents that interact with ergosterol. But, in this case, they act as inhibitors of squalene epoxidase, blocking the conversion of squalene into 2,3-oxidosqualene, that result in ergosterol depletion and accumulation of toxic sterols. It was shown that the increasing of the squalene levels is toxic, leading to cell membrane permeability and then disrupting the cellular organization (Ghannoum and Rice, 1999; White et al., 1998). However, this class of antifungal drugs presents a weak activity against the most frequent *Candida* species, being only active against dermatophytes (Kontoyiannis and Lewis, 2002; Sanglard, 2002).

On the other hand, fluoropyramidines and echinocandins act differently from the previous drugs; the first act as inhibitor of nucleic acids, while the second as inhibitor of the glucan synthesis and, therefore, are effective against *Candida* biofilm cells (Kontoyiannis and Lewis, 2002; Pereira Gonzales and Maisch, 2012). Fluoropyrimidines, namely 5-fluorocytosine (5FC), is a fluorinated pyrimidine that impairs nucleic acid biosynthesis due to the formation of toxic fluorinated pyrimidine antimetabolites. A permease enzyme aids 5FC to enter on fungal cells, where it is converted into 5-fluorouracil (5FU), catalyzed by the cytosine deaminase. After this, 5FU is converted into 5-fluorouridylic acid (FUMP) and, then, phosphorylated and incorporated into RNA, leading to a disruption of protein synthesis. Another mechanism of action of 5FU, results of its conversion into 5-fluorodeoxyuridine monophosphate, a potent inhibitor of the enzyme involved in DNA synthesis and nuclear division (Waldorf and Polak, 1983). There are some studies that refer an increasing resistance to 5FC (Ghannoum and Rice, 1999; Gubbins and Anaissie, 2009; Liu et al., 2009; Souza et al., 2010), and despite several mechanisms of action responsible for 5FC resistance are still not established, they could be related with losses of permease activity or decrease

of enzymatic activity responsible for the conversion of 5FC into FMUP. This process was observed in *C. glabrata*, while mutational losses of one of the pyrimidine salvage enzymes and decrease in UPRTase in a gene dose-dependent manner were observed in *C. albicans* strains, resistant to 5FC (Ghannoum and Rice, 1999).

Lastly, echinocandins (i.e. caspofungin, anidulofungin, and micafungin) are the latest and, at the same time, the first new class of antifungal drugs. The main target of this drug is the fungal cell wall, acting as inhibitors of the α-1,3-D-glucan biosynthesis by blocking of β-1,3-D-glucan synthase (Perlin, 2014; Sanglard and Odds, 2002). Despite a higher level of efficiency associated to this class of antifungal drugs, exerting rapid fungicidal effects against *Candida* species, including azole-resistance species (Kontoyiannis and Lewis, 2002), in the last years, it has been observed an increasing level of resistance, namely for *C. albicans, C. glabrata, C. krusei* and *C. parapsilosis* (Kanafani and Perfect, 2008; Perlin, 2009). The involved resistance mechanisms were not completely elucidated and other are still unknown; however, drug tolerance conferred by adaptive cellular physiology to the environmental stress, as well as genetic mutations and amino acids substitutions are the main supposed contributors associated with *Candida* species echinocandin-resistant (Perlin, 2009).

Nevertheless, new perspectives of development of new orally effective drugs are open and different experiments have been made (Kanafani and Perfect, 2008; Perlin, 2014, 2009; Sanglard, 2002). So, considering all the advances on antifungal drugs research, it is necessary to take into account the safety, tolerability, efficacy, toxicity and, even side effects of these substances/chemical molecules. In this sense, other alternatives safer than the current antifungal drugs are necessary.

3. Active principles of plants

3.1. Plants as a rich source of bioactive compounds

Plants have been used for several generations in traditional herbal medicine, as first choice treatment. The first civilizations established the therapeutic potential of plants taking into account the more or less prominent effects observed in the body. They also observed that certain plants evidenced toxic effects according to the dose. However, they did not know the reasons that provided those effects, as well as, the nature of plant constituents. Thus, much of the knowledge was empirical, passing from generation to generation, but lacking of a solid foundation of the use and prescription, mostly due to the low literacy and written information (Halberstein, 2005; Murray and Pizzorno, 1998; Petrovska, 2012).

Currently, it is well recognized that hundreds of biological active chemical compounds are present, in each plant, working in synergism, and conferring a broad variety of bioactivities, being subject of an increasing scientific interest. More and more, people worldwide use medicinal plants as first priority to maintain a good health, to prevent or even treat some health conditions. Linked to this, some studies have been conducted, using a wide variety of plants, towards the identification of bioactive molecules, their properties and mechanisms of action (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). In fact, natural matrices, in particular, plants, are extremely rich sources of biomolecules that have sparked an increasing interest for scientific researchers, in different areas of knowledge. Until now, several chemical compounds have been identified, but only a few properties have been clarified, with many remaining undefined. Nevertheless, many compounds are still unknown, as also

the synergic interactions among them (Carocho and Ferreira, 2013a; Choudhary and Atta-ur-Rahmant, 1999; Devasagayam et al., 2004; Rubió et al., 2013).

It is truly believed that the biologically active chemical compounds present in plants act synergistically and confer, both direct and indirect effects, to the human body. The direct impact is commonly due to their phytopharmacological action, while the indirect impact is linked to the simultaneous interaction with other plants or drugs. Furthermore, it should be highlighted that, the fact that one plant from a particular genus contains a specific chemical composition and a significant medicinal value does not mean that all the other plants from the same genus had the same value. Even some studies report that the same species, but with different origins might have considerable differences on chemical composition and, therefore, a different efficacy and potency in the bioactivity (Farhat et al., 2009, 2013; Ghasemi Pirbalouti et al., 2013; Papageorgiou et al., 2008; Politeo et al., 2006).

In the modern medical classification, a plant acquire the "medicinal" status when it presents several pharmacologically active compounds, making possible its use at a therapeutic level, conferring not only benefits in the treatment of some conditions, but also in prevention/prophylaxis (Balch, 2006; Murray, 2004; Murray and Pizzorno, 1998). Notwithstanding, other chemical compounds present in trace amounts, could influence the action of the main molecules, which explains the higher potential of using the whole natural matrix instead of an isolate chemical compound (Ettefagh et al., 2011; Junio et al., 2011).

Thus, it is very important to provide a correct and complete characterization of the bioactive compounds present in medicinal plants, in order to complement and unify the prescriptions and, at the same time, to establish the amount/dosage of active principles needed to treat/avert various health problems. Currently, due to the advances of the

analytical methods, it was possible to elucidate the structure of thousands of phytochemicals, either primary or secondary metabolites (**Figure 1**).

3.2. Primary metabolites

Primary metabolites comprise the organic compounds derived from the primary metabolism of plants; they are often concentrated in seeds and/or vegetative organs and play an important role in the physiological development and basic cell metabolism. In general, these compounds are not limited to the plant kingdom, being even used in several biosynthetic pathways (Nelson and Cox, 2000).

Higher plants are able to synthetize organic compounds and produce oxygen from the light, water and carbon dioxide, which are the main energetic and food sources for animals. Furthermore, these same organic compounds are also an energetic source for biosynthetic organisms. This process, in which autotrophic organisms produce organic compounds according to their needs, is commonly known as photosynthesis: light phase and dark phase. Organic compounds are synthetized in the dark phase, through some biosynthetic pathways (Nelson and Cox, 2000). Proteins, lipids, carbohydrates and chlorophyll are the main compounds derived from the primary metabolism (**Figure 1**).

Besides many other physiological functions, proteins and even some free amino acids are considered crucial transport elements of a wide variety of molecules; integrate the genetic material binding to nucleic acids; include enzymes; play an important reserve role and confer high protection against invaders (Nelson and Cox, 2000; Proença da Cunha et al., 2010, 2012). On the other hand, lipids, commonly defined as water insoluble compounds but soluble in organic solvents, play important organic benefits as structural components of cellular membranes; energetic reserve; protective function; hormonal regulators and synthesizers of inflammatory immunomodulators (eicosanoids:

prostaglandins, thromboxanes and leukotrienes), among other crucial functions in living organisms (Campos, 2008; Nelson and Cox, 2000).

Carbohydrates, or glycids, represent the basis of dietary food of a majority of living organisms. According to the length and the type of glycosidic linkages, these molecules play different biological properties and have innumerous applications. One of the most common is their energetic cellular reservoir function, being accumulated in the main reserve organs of plants – seeds, grains and tubers, as well as leaves. The latest have a limited storage capacity (Campos, 2008; Nelson and Cox, 2000; Proença da Cunha et al., 2010).

Lastly, chlorophyll, a green pigment mainly present in the higher plant protoplasts, but also in red algae and purple bacteria, essentially exerts functions of photosynthetic pigments. Despite the existence of two types of chlorophyll, *a* and *b*, both of them are involved in organic compounds synthesis and, therefore, in the primary function of plants: nutrition (Campos, 2008; Nelson and Cox, 2000).

In fact, primary metabolites are much more than merely macronutrients. Some of the bioactive properties reported for plants, such as antioxidant, antimicrobial, anti-inflammatory, and antitumor activities, have been related with primary metabolites, mainly lipids (polyunsaturated fatty acids, sterols), proteins, carotenoids, vitamins and carbohydrates (polysaccharides and glycosides) (Ksouri et al., 2012).

3.3. Secondary metabolites

Secondary metabolites are organic compounds that derived from the primary metabolites of plants. It is well established that these metabolites play specialized functions in a wide variety of living organisms, being even considered as biologically active compounds. They are renowned as possess higher value than the primary

metabolites, in relation to the life expectancy, wellbeing and even to prevent/avert some diseases/disorders (Nelson and Cox, 2000; Rubió et al., 2013).

Terpenes are a class of secondary metabolites formed by several isoprene units, i.e. several combinations of 5-carbon-base (C5). Different combinations of the isoprene units originate structurally and functionally different classes of terpenes (Rubió et al., 2013). Thus, they could occur as monoterpenes (C10), diterpenes (C20), triterpenes (C30), tetraterpenes (C40), but also hemiterpenes (C5) and sesquiterpenes (C15). Monoterpenes and diterpenes are the main classes of terpenes present on herbs and spices. Furthermore, these compounds have important biological activities, including antimicrobial properties against a wide variety of pathogens such as *Candida* species (Alves et al., 2013; Rubió et al., 2013; Saleem et al., 2010).

Steroids are secondary metabolites derived from the tetracyclic triterpenes (C30), composed by isoprenoid C5 units derived from isopentenyl (3-methylbut-3-en-l-yl) pyrophosphate, and presenting a characteristic branched chain structure. Stigmasterol has been reported as one of the most abundant steroids in plant oils. These compounds are commonly highly degraded into other products, namely steroid hormones, that play important organic functions (Carocho and Ferreira, 2013b; Nelson and Cox, 2000). Moreover, the antimicrobial activity of steroids has also been described, including the antifungal properties against some pathogens such as *Candida* species (Alves et al., 2013; Saleem et al., 2010; Sanglard, 2002). One of the proposed mechanisms of action is their ability to disrupt membrane integrity (Saleem et al., 2010), but others remain unclear and even unknown.

Alkaloids comprise a diverse group of heterocyclic nitrogen substances, being commonly considered high toxic molecules that play an important defensive role, but reflecting a general biological principle of poisonous plants (Inbaraj et al., 2001, 2006;

Sertel et al., 2011). Nevertheless, in some situations, their toxicity is benefic; for example, Sertel et al. (2011) reported that vinblastine, vincristine (from *Catharanthus roseus*, formerly: *Vinca rosea*) and semisynthetic vindesine and vinorelbine, presented high cytotoxicity against cancer cells, highlighting the potential of these dimeric indole alkaloids for cancer, leukemia and lymphomas treatments. The efficacy of alkaloids against bacteria, parasites, dermatophytes and fungi, including *Candida* species, has also been described (Ali-Shtayeh and Ghdeib, 1999; Arif et al., 2011, 2009; Carocho and Ferreira, 2013b; Dzoyem et al., 2014; Rose, 1999; Sher, 2009; Silva and Fernandes Júnior, 2010; Wyk et al., 2009; Xie et al., 2012). The intercalation into cell wall and/or DNA is considered one of the main described mechanisms of bioactive action of alkaloids (Silva and Fernandes Júnior, 2010).

Phenolic compounds constitute a major class of plant secondary metabolites being broadly distributed, with more than 8000 phenolic structures currently identified. These compounds can contain one or more aromatic rings with one or more hydroxyl groups (Dai and Mumper, 2010). In fact, the term “phenolic” or “polyphenol” can be chemically defined as a substance which possesses an aromatic ring bearing at least one (phenol) or more (polyphenol) hydroxyl substituent, including functional derivatives (esters, methyl ethers, glycosides, etc.), ranging from simple molecules, such as phenolic acids, to high complex structures, such as tannins (Dai and Mumper, 2010; Santos-Buelga et al., 2012). In the modern classification, the broad category of phenolics is divided into several groups, according to the number of phenol subunits present: polyphenols and simple phenols. Thus, polyphenols possessing at least two phenol subunits are classified as flavonoids, while those compounds which possess three or more phenol subunits are included in tannins (hydrolysable and non-hydrolysable) (Giada, 2013; Robbins, 2003). Phenolic acids, flavonoids and tannins are

the most common, being stilbenes and lignans less common (Dai and Mumper, 2010). Curiously, these classes of phenolic compounds are currently the main subjects of scientific researches. But, beyond these, other phenolic compounds, like chalcones, coumarins, xanthones and lignins, are also present in natural matrices (**Figure 2**).

Several researchers have demonstrated the antioxidant potential of phenolic compounds (Çekiç et al., 2013; Rice-Evans et al., 1996; Walch et al., 2011), but currently other bioactive properties have also been studied. Curiously, some of these biological properties are directly linked to the antioxidant activity. It is a fact, that the chemical structure of phenolic compounds determine their properties as well as mechanism of action, being conferred by different ways (Giada, 2013). Nevertheless, and not less important, is the fact that despite Reactive Oxygen and Nitrogen Species (ROS/RNS) at physiological concentrations may be required for normal cell functioning and to play an important role in plant and animal evolutions, these species are able to attack biological macromolecules (e.g., cellular DNA), causing a wide variety of cellular damages, disorders and even diseases; to disestablish of the defense systems increasing the vulnerability to infections by pathogens, parasites and other invaders (Carocho and Ferreira, 2013a; Çekiç et al., 2013; Chaturvedi and Beal, 2013; Devasagayam et al., 2004; Valko et al., 2007).

4. Activity of phenolic extracts/compounds against *Candida* species

4.1. The use of phenolic extracts against Candida species

Several studies have been performed in order to evaluate the antifungal potential of polar extracts from plant origin, which are enriched in phenolic compounds, such as acetone (**Table 1**), aqueous (**Table 2**), ethanolic (**Table 3**), methanol-dichloromethane (**Table 4**), methanolic (**Table 5**), hydroalcoholic (methanol: or ethanol: water mixtures)

(**Table 6**), DMSO, diethyl ether and ethyl acetate extracts, and tinctures (**Table 7**). The aqueous extracts were the most studied preparations, followed by methanolic and ethanolic extracts.

Different techniques/assays have been used for that purpose. Agar disc diffusion and broth dilution (microdilution and macrodilution) methods are the most commonly used, being, normally, performed according to the Clinical and Laboratory Standards Institute (CLSI), with some modifications. Both of them are considered antimicrobial susceptibility tests, expressing the results as halo inhibition zones or minimal inhibitory (MIC) and minimal fungicidal (MFC) concentrations, respectively. The most tested *Candida* species were *C. albicans, C. tropicalis, C. krusei, C. glabrata, C. parapsilosis, C. lusitaniae* and *C. guilliermondii*, being considered the main species associated to opportunistic fungal infections (Vázquez-González et al., 2013).

In general, the plant extracts obtained using methanol and water, as solvent extraction, and mixtures of the previous (hydroalcoholic extracts) were more effective against *Candida* species than the other extracts prepared with a unique solvent. Thus, the methanol (**Table 5**), aqueous (**Table 2**) and hydroalcoholic extracts (ethanol: water and methanol: water mixtures) (**Table 6**) presented lower MICs than the extracts obtained with acetone (**Table 1**), methanol-dichloromethane (**Table 4**) ethanol (**Table 3**) or other extracts (**Table 7**). For example, hydroalcoholic extracts of *Cassia fistula* (MIC=0.025 mg/mL), *Emblica officinalis* (MIC=0.1024 mg/mL), *Glycyrrhiza glabra* (MIC=0.512 mg/mL) and *Punica granatum* (MIC=0.0039 mg/mL) presented a higher antifungal effect, against *C. albicans*, than the extracts of the same plant species prepared with a single solvent. The only exceptions were the aqueous extracts of *Sapindus saponaria* (MIC=0.16 mg/mL), against *C. parapsilosis*, and *Syzygium aromaticum* (MIC=0.003125 mg/mL), against *C. tropicalis*, that gave a higher effect than its

hydroalcoholic extracts, and the methanolic extract of *Salvia officinalis* (MIC=0.16 mg/mL) that evidenced a higher antifungal potential, against *C. tropicalis*, than the hydroalcoholic (MIC=1.25 mg/mL) and aqueous (MIC=1.25 mg/mL) extracts. Notwithstanding, the number of studies that report antifungal properties of hydroalcoholic extracts is lower than the studies using methanol, ethanol or water.

Comparing the antifungal potential of the extracts prepared with a unique solvent, the methanolic extracts (**Table 5**) showed the lowest MICs for the majority of the *Candida* species, followed by aqueous (**Table 2**) and ethanolic (**Table 3**) extracts. In particular, *Adiantum capillus veneris, Artemisia herba-alba, Capparis spinosa, Eucalyptus sideroxylon, E. torquata, Glycyrrhiza glabra, Laurus nobilis, Pimpinella anisum* and *Salvia officinalis* methanolic extracts showed higher antifungal potential than their aqueous and ethanolic extracts. On the other hand, *Acorus calamus, Funtumia elastica, Hyssopus officinalis* subsp. *pilifer, Murraya koenigii, Ribes nigrum* and *Zingiber officinalis* aqueous extracts evidenced most pronounced antifungal effects than their ethanolic and methanolic extracts. *Allium sativum, Aloe barbadensis, Aloe excelsa, Cinnamomum* spp. and *Solanum nigrum* aqueous and ethanolic extracts evidenced similar potential against *Candida* species. Lastly, *Camellia sinensis, Cassia alata, Mallotus oppositifolius, Morinda morindoides, Origanum vulgare, Plantago media, Punica granatum, Quercus infectoria, Rhus angustifolia, Sclerocarya birrea* and *Thymus kotschyana* ethanolic extracts evidenced higher antifungal potential than aqueous and methanolic extracts.

In specific plant species, the tendency described was modified. For example, the methanol-dichloromethane extract of *Andrographis paniculata* showed a higher antifungal potential than their ethanolic and methanolic extracts; ethanol, acetone, diethyl ether and ethyl acetate extracts of *Origanum vulgare*, as well as aqueous and

ethyl acetate extracts of *Hyssopus officinalis* subsp. *Pilifer* and aqueous and hydroalcoholic extracts of *Salvia officinalis* showed similar antifungal effects. Furthermore, *Crossandra infundibuliformis* ethyl acetate and methanol extracts showed similar effects, whereas *Gonzalagunia rosea* and *Montanoa* methanolic extracts showed higher antifungal potential than the corresponding methanol: dichloromethane extracts; the acetone extract of *Paullinia cupana* seems to be more effective than the ethanolic extract against *C. albicans*, but due to the differences in the units used to express the results, it is difficult to compare both values.

Analysing the antifungal activity against specific *Candida* species, hydroalcoholic extracts showed the most pronounced properties against *C. albicans*, followed by methanolic and methanol-dichloromethane extracts. *Punica granatum* hydroalcoholic (ethanol:water, 50:50 v/v) extract revealed the highest antifungal activity (MIC = 0.0039 mg/mL). In general, methanolic extracts followed by aqueous and hydroalcoholic extracts, showed a higher antifungal potential against *C. glabrata* than the ethanolic and methanol-dichloromethane extracts. *Dorstenia turbinata* (0.039 mg/mL) and *Thymbra spicata* (0.01 mg/mL) methanolic extracts evidenced the most pronounced effects. For *C. guilliermondii*, the hydroalcoholic extract of *Syzygium aromaticum* (MICs = 0.05 mg/mL) was the most effective preparations, but *Punica granatum* ethanolic extract (MIC = 0.125 mg/mL) also evidenced a lower MIC value. For *C. krusei*, the methanolic extracts were the most efficient plant extract preparations, followed by ethanolic and aqueous extracts. *Thymbra spicata* (MIC = 0.01 mg/mL) and *Laurus nobilis* (MIC = 0.07 mg/mL) comprises the methanolic extracts that evidenced highest antifungal activity against *C. krusei*. Concerning *C. lusitaniae*, aqueous extracts presented the highest antifungal potential, followed by ethanolic, methanol-dichloromethane and ethyl acetate extracts. *Epilobium augustifolium* aqueous extract

(MIC = 0.05 mg/mL) revealed to be the best against *C. lusitaniae*. On the other hand, to the *C. parapsilosis,* the hydroalcoholic extracts were the most effective preparations, followed by methanolic, aqueous and ethanolic extracts. *Punica granatum* hydroalcoholic extract (MIC = 0.0039 mg/mL) presented the most pronounced antifungal potential against *C. parapsilosis*. Lastly, aqueous extracts were the most efficient plant extract preparations against *C. tropicalis*, followed by methanolic, methanol-dichloromethane and hydroalcoholic extracts. *Syzygium aromaticum* (MIC=0.003125 mg/mL) aqueous extract revealing the highest potential.

It can be concluded that the type of solvent used in the extraction of the phytochemicals (including phenolic compounds) has influence in the final composition of the extract and, consequently, in the bioactivity. Nevertheless, the *Candida* species, as also the strains used, had also influence in the antifungal results. Several studies have highlighted some aspects involved in the mechanisms of action such as interaction with the lipid bilayer of the cell membrane, which consequently affect the membrane permeability, respiratory chain and cellular energy production (Tintino et al., 2014), as well as the inhibition of the H^+-ATPase (Kuete et al., 2010). Beyond that, it is possible to distinguish the antifungal potential, between fungistatic and/or fungicidal. The majority of the studies reported fungistatic effects of plant extracts (Anibal et al., 2013; Barros et al., 2013a; Basile et al., 2013; Correa-Royero et al., 2010; Dzoyem et al., 2014; Kariba et al., 2001; Kim and Lee, 2012; Kurdelas et al., 2010; Lubian et al., 2010; Nordin et al., 2013; Pathak, 2012; Thirach et al., 2003; Tomczykowa et al., 2008; Tsuzuki et al., 2007), but there are also some reports evidencing fungicidal effects, most of them in a dose-dependent manner (Askun et al., 2008; Barros et al., 2013a; Dzoyem et al., 2014; Korukluoglu et al., 2008; Lubian et al., 2010; Nordin et al., 2013; Rajeh et al., 2010; Siler et al., 2014; Sule et al., 2012; Yazdani et al., 2009).

It is crucial to characterize the phytochemical composition of the plant extracts with antifungal activity, in order to identify the individual compounds responsible for this bioactivity, and to elucidate the main molecular targets in *Candida* species. Some studies have been performed in individual phenolic compounds (one of the most abundant molecules in polar extracts), as it will be discussed in the next section but, unfortunately, the majority of the studies report anti-*Candida* activity of crude extracts without any chemical characterization.

4.2. The use of phenolic compounds against Candida species

Phenolic acids, flavonoids and tannins are the most studied groups of phenolic compounds, comprising molecules with evidenced antifungal properties. These molecules have been isolated from different plant sources, as also commercially obtained as pure compounds.

A commercial sample of gallic acid presented higher antifungal potential against *C. albicans* than the same compound isolated from *Lythrum salicaria*, *Paeonia rockii* or *Pelargonium reniforme* subsp. *reniforme* (**Table 8**). The same behavior was observed for commercial quercetin, in comparison to the one obtained from *Buddleja salviifolia* and *Halimodendron halodendron* (**Table 9**). On the other hand, commercial sample of salicylic acid presented lower antifungal potential than the same compound isolated from *Halimodendron halodendron* (**Table 8**). It would be expected a similar bioactivity for the same compound, independently of its source. Therefore, the observed differences are probably related with the purity grade of the tested compounds, as well as with the vehicles/solvents used to test antifungal activities.

Table 8 shows the activity of phenolic acids (hydroxycinnamic acid derivatives, hydroxybenzoic acid derivatives and other related compounds) against *Candida* species.

In general, hydroxycinnamic acid derivatives presented lower MICs against *Candida* species, than the hydroxybenzoic acid derivatives. The only exception was reported by Faria et al. (2011); however, in this case, it is necessary to take into account that the results referred to tested concentrations and not MIC values.

Analyzing the results by each *Candida* species, in general, commercial compounds, mainly albicanyl caffeate (MIC = 4 µg/mL) presented the most pronounced antifungal effects against *C. albicans*. Two phenolic acid related compounds, dihydro-N-caffeoyltyramine and *trans*-N-caffeoyltyramine (MICs = 5 µg/mL) obtained from *Lycium chinense* also evidenced a significant potential, followed by gallic acid isolated from *Paeonia rockii* (30 µg/mL) and gentisic, syringic, vanillic and 4-*O*-β-D-(6-*O*-gentisoylglucosyl)vanillic acids from *Stenoloma chusanum* (50 µg/mL). Regarding other *Candida* species, only Latte & Kolodziej (2000) report the antifungal activity of gallic acid from *Pelargonium reniforme* subsp. *reniforme* against *C. glabrata* (MIC =62 µg/mL) and *C. krusei* (MIC = 125 µg/mL). To authors' knowledge there are only reports regarding commercial compounds against *C. parapsilosis, C. tropicalis* and *C. lusitaniae*.

The antifungal activity of flavonoids against *Candida* species is presented in **Table 9**. Commercial compounds displayed slight higher antifungal effects than flavonoids isolated from plant sources. Among the commercial compounds, silibinin (MIC=4 µg/mL), a flavolignan, exerted the most pronounced antifungal activity, against *C. albicans*, followed by apigenin (a flavones), genistein (an isoflavone), naringin (a flavanone), quercitin (a flavonol) and silymarin (a flavolignan), which presented similar potential (MIC=8 µg/mL). Concerning to the flavonoids derived from plant origin, 2'-*O*-Methyllabronisoflavone (16-25 µg/mL) and 9-*O*-methyl-4-hydroxyboeravinone B (48 µg/mL), two isoflavones isolated from *Mirabilis jalapa,* also presented a

pronounced antifungal potential against *C. albicans*, followed by the flavonols kaempferol, myricetin, quercitin and rutin from *Origanum vulgare* subsp. *gracile* and *Origanum acutidens* (except quercetin and rutin). In general, flavonols (mainly represented by kaempferol, myricetin and quercetin), followed by flavanones and flavolignans, were the most effective antifungal flavonoids against *Candida* species. Once again, *C. albicans* was the main studied *Candida* species, being only tested commercial flavonoids against *C. parapsilosis* and compounds isolated from *Origanum* species against *C. glabrata*.

Table 10 shows the antifungal activity of hydrolyzable tannins, stilbenes and xanthones against *Candida* species. Comparing the different hydrolyzable tannins isolated from *Pelargonium reniforme* subsp. *reniforme,* it is possible to conclude that similar antifungal effects were achieved; the obtained MIC values were the same for corilagin, glucogallin, methyl ester, pelargoniin and phyllantusiin, against *C. albicans, C. glabrata* and *C. krusei*. Comparing *Pelargonium reniforme* subsp. *reniforme* with *Punica granatum*, the hydrolyzable tannin, punicalagin, exerted higher antifungal effect against *C. albicans* (~128 times higher). Regarding stilbenes, resveratrol and 3,4'-difluorostilbene gave similar MIC values against *C. albicans* (Sun et al., 2004), while for xanthones the commercial compound mangiferin presented a more pronounced effect against *C. albicans*. 8-Carboxy-methyl-1,3,5,6-tetrahydroxyxanthone gave significantly different MIC values for each *Candida* species; *C. krusei* and *C. parapsilosis* were the most sensible to the mentioned compound (15.7 µg/mL), while *C. albicans* showed higher resistance (62.5 µg/mL). Among tannins, stilbenes and xanthones, the latter seem to be the most efficient, exhibiting lower MICs against *Candida* species.

Overall, commercial compounds seem to be more efficient than phenolic compounds isolated from natural matrices probably due to their higher purity grade. Regarding phenolic compounds from natural sources, punicalagin (isolated from *Punica granatum*), followed by dihydro-N-caffeoyltyramine and *trans*-N-caffeoyltyramine (isolated from *Lycium chinense*), were the most efficient against *C. albicans*. The hydrolyzable tannins, carolagin, glucogallin, methyl ester, pelargonin and phyllantusiin (isolated from *Pelargonium reniforme* subsp. *reniforme*) were the most efficient for *C. glabrata*, while 8-carboxy-methyl-1,3,5,6-tetrahydroxyxanthone, a xanthone isolated from *Leiothrix spiralis*, was the most effective against *C. krusei* and *C. tropicalis*. Lastly, for *C. parapsilosis*, punicalagin (isolated from *Punica granatum*), followed by 8-carboxy-methyl-1,3,5,6-tetrahydroxyxanthone (isolated from *Leiothrix spiralis*), presented the most pronounced effects.

5. Conclusions

Being part of the commensal flora, *Candida* species are also related to several situations of overgrowth, and an increasing resistance to the current antifungal drugs has been observed. Despite the efforts in order to discover and/or synthetize new chemical molecules, more efficient and effective than the existents, it is necessary to consider that these compounds could be associated to a wide variety of side effects. Beyond that, those experiments are very expensive and take a long time until the accreditation/commercialization of the products. Medicinal plants are used since ancient times and present several bioactive properties, due to their richness in some biomolecules, such as phenolic compounds. Several studies have been developed towards investigating the antifungal properties of phenolic compounds enriched extracts, against *Candida* species. For that, different extraction solvents have been used,

namely, water, ethanol, methanol, methanol-dichloromethane and even mixtures of the previous. In parallel, and due to the high antifungal potential evidenced by some plant extracts, an increasing number of studies have been evaluating the antifungal potential of phenolic compounds isolated from those matrices.

Despite the existence of a tenuous variation on the antifungal activity according to *Candida* species, in general, the plant extracts obtained using methanol, water and mixtures of the previous (hydroalcoholic extracts) were more effective against *Candida* species than the extracts prepared using a unique solvent. This higher antifungal activity might be related with the solubility of the active principles in the solvents used; phenolic compounds are one of the most abundant bioactive molecules present in those polar extracts. Hydrolysable tannins, followed by some phenolic amides and flavonoids seem to exert the most pronounced anti-*Candida* effects. There are some evidences that the mentioned extracts/compounds affect fungal cells through interaction with the lipid bilayer of the cell membrane. They could act by disrupting the membrane integrity or by intercalation into cell wall and/or DNA. Nevertheless, much more studies are necessary not only to evaluate the antifungal potential of the reviewed and other medicinal plants, but also to establish clearly mechanisms of action involved in potential of phenolic compounds from plant origin against *Candida* species, as also validate the results by *in vivo* studies.

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Table 1. Activity of acetone extracts against *Candida* species

Plant source	***Candida* species**	**MIC**	**References**
Combretum albopunctatum	*C. albicans*	0.64 mg/mL	(Masoko et al., 2010)
Combretum imberbe	*C. albicans*	2.5 mg/mL	(Masoko et al., 2010)
Combretum nelsonii	*C. albicans*	0.04 mg/mL	(Masoko et al., 2010)
Origanum vulgare	*C. albicans*	5 mg/mL	(Ličina et al., 2013)
Paullinia cupana	*C. albicans*	250 µm/mL	(Basile et al., 2013)
Sclerocarya birrea	*C. parapsilosis*	0.32 mg/mL	(Masoko et al., 2008)
Terminalia sericea	*C. albicans*	0.64 mg/mL	(Masoko et al., 2010)

MIC - Minimum inhibitory concentration.

Table 2. Activity of aqueous extracts against *Candida* species

Plant source	***Candida* species**	**MIC**	**References**
Acorus calamus	*C. albicans*	12.5 mg/mL	(Webster et al., 2008)
	C. krusei	12.5 mg/mL	
	C. lusitaniae	12.5 mg/mL	
	C. parapsilosis	12.5 mg/mL	
Adiantum capillus veneris	*C. albicans*	1 mg/mL*	(Ishaq et al., 2014)
Allium sativum	*C. albicans*	0.2 mg/mL	(Shamim et al., 2004)
		100 mg/mL*	(Fei et al., 2008)
		1 mg/mL*	(Pathak, 2012)
	C. dublinensis	1 mg/mL*	(Pathak, 2012)
	C. grabrata	0.2 mg/mL	(Shamim et al., 2004)
		1 mg/mL*	(Pathak, 2012)
	C. krusei	100 mg/mL*	(Fei et al., 2008)
		1 mg/mL*	(Pathak, 2012)
	C. tropicalis	0.2 mg/mL	(Shamim et al., 2004)
		100 mg/mL*	(Fei et al., 2008)
		1 mg/mL*	(Pathak, 2012)
Alnus viridis	*C. albicans*	12.5 mg/mL	(Webster et al., 2008)
	C. glabrata	25 mg/mL	
	C. krusei	0.2 mg/mL	
	C. lusitaniae	6 mg/mL	
	C. parapsilosis	25 mg/mL	
	C. tropicalis	3 mg/mL	
Aloe barbadensis	*C. albicans*	1 mg/mL	(Shamim et al., 2004)
	C. grabrata	1 mg/mL	
	C. tropicalis	0.2 mg/mL	
Aloe excelsa	*C. albicans*	1 mg/mL	(Coopoosamy and Magwa, 2007)
	C. tropicalis	0.2 mg/mL	
Arbutus unedo	*C. albicans*	10 mg/mL*	(Dib et al., 2010)
Arctium minus	*C. albicans*	12.5 mg/mL	(Lubian et al., 2010)
	C. dubliniensis	12.5 mg/mL	
	C. glabrata	12.5 mg/mL	
	C. krusei	12.5 mg/mL	

	C. stellatoideia	12.5 mg/mL	
	C. tropicalis	25 mg/mL 12.5 mg/mL	
Artemisia campestris	*C. glabrata*	25 mg/mL	(Webster et al., 2008)
	C. krusei	50 mg/mL	
	C. lusitaniae	25 mg/mL	
	C. parapsilosis	50 mg/mL	
	C. tropicalis	25 mg/mL	
Artemisia frigida	*C. glabrata*	0.4 mg/mL	(Webster et al., 2008)
	C. krusei	6 mg/mL	
	C. lusitaniae	12.5 mg/mL	
	C. parapsilosis	50 mg/mL	
	C. tropicalis	6 mg/mL	
Azadirachta indica	*C. albicans*	1 mg/mL*	(Pathak, 2012)
	C. dublinensis	1 mg/mL*	
	C. glabrata	1 mg/mL*	
	C. krusei	1 mg/mL*	
	C. tropicalis	1 mg/mL*	
Betula alleghaniensis	*C. albicans*	0.8 mg/mL	(Webster et al., 2008)
	C. glabrata	0.05 mg/mL	
	C. krusei	0.4 mg/mL	
	C. lusitaniae	0.4 mg/mL	
	C. parapsilosis	3 mg/mL 0.05 mg/mL	
	C. tropicalis	6 mg/mL	
Brucea javanica	*C. albicans*	50 mg/mL	(Nordin et al., 2013)
	C. dubliniensis	3.13 mg/mL	
	C. glabrata	25 mg/mL	
	C. krusei	50 mg/mL	
	C. lusitaniae	25 mg/mL	
	C. parapsilosis	25 mg/mL	
	C. tropicalis	50 mg/mL	
Cassia alata	*C. albicans*	26.90 mg	(Timothy et al., 2012)
Camellia sinensis	*C. albicans*	10 mg/mL*	(Doddanna et al., 2013)
Cinnamomum sp.	*C. albicanus*	200 mg/mL*	(Qader et al., 2013)
	C. dublicans	200 mg/mL*	
	C. glabrata	200 mg/mL*	
	C. krusei	200 mg/mL*	
	C. tropicalis	200 mg/mL*	
Emblica officinalis	*C. albicans*	200 mg/mL*	(Saeed and Tariq, 2007)
Epilobium augustifolium	*C. albicans*	0.2 mg/mL 0.4 mg/mL 0.4 mg/mL 0.4 mg/mL	(Webster et al., 2008)
	C. glabrata	0.025 mg/mL	
	C. krusei	0.2 mg/mL	

	C. lusitaniae *C. parapsilosis* *C. tropicalis*	0.05 mg/mL 0.4 mg/mL 0.1 mg/mL 1.6 mg/mL	
Eucalyptus sideroxylon	*C. albicans*	400 mg/mL*	(Ashour, 2008)
Eucalyptus torquata	*C. albicans*	400 mg/mL*	(Ashour, 2008)
Fragaria virginiana	*C. albicans* *C. glabrata* *C. krusei* *C. lusitaniae* *C. parapsilosis* *C. tropicalis*	0.8 mg/mL 0.05 mg/mL 0.05 mg/mL 0.1 mg/mL 0.2 mg/mL 0.8 mg/mL	(Webster et al., 2008)
Funtumia elastica	*C. albicans*	100 mg/mL*	(Adekunle and Ikumapayi, 2006)
Hyssopus officinalis subsp. *pilifer*	*C. albicans*	7.00 mg/mL	(Džamić et al., 2013)
Lonicera japonica	*C. albicans*	Viability (%): 81.48	(Wong and Tsang, 2009)
Mallotus oppositifolius	*C. albicans*	100 mg/mL*	(Adekunle and Ikumapayi, 2006)
Morinda citrifolia	*C. albicans*	40 mg/mL	(Jainkittivong et al., 2009)
Morinda morindoides	*C. albicans*	62.50 mg/mL	(Touré et al., 2011)
Murraya koenigii	*C. albicans* *C. dublinensis* *C. glabrata* *C. krusei* *C. tropicalis*	1 mg/mL* 1 mg/mL* 1 mg/mL* 1 mg/mL* 1 mg/mL*	(Pathak, 2012)
Ocimum sanctum	*C. glabrata*	1 mg/mL*	(Pathak, 2012)
Origanum vulgare	*C. albicans*	200 mg/mL*	(Abdul et al., 2012)
		20 mg/mL	(Ličina et al., 2013)
Paeonia suffruticosa	*C. albicans*	Viability (%): 100.53	(Wong and Tsang, 2009)
Plantago media	*C. albicans* *C. dublicans* *C. glabrata* *C. krusei* *C. tropicalis*	200 mg/mL* 200 mg/mL* 200 mg/mL* 200 mg/mL* 200 mg/mL*	(Qader et al., 2013)
Populus tremuloides	*C. albicans*	1.6 mg/mL	(Webster et

	C. glabrata	0.025 mg/mL	al., 2008)
	C. krusei	0.2 mg/mL	
	C. lusitaniae	0.2 mg/mL	
	C. parapsilosis	0.4 mg/mL	
	C. tropicalis	1.6 mg/mL	
Punica granatum	*C. albicans*	200 mg/mL*	(Qader et al., 2013)
	C. dublicans	200 mg/mL*	
	C. glabrata	200 mg/mL*	
	C. krusei	200 mg/mL*	
Quercus infectoria	*C. albicans*	200 mg/mL*	(Qader et al., 2013)
	C. dublicans	200 mg/mL*	
	C. glabrata	200 mg/mL*	
	C. krusei	200 mg/mL*	
	C. tropicalis	200 mg/mL*	
Rhus angustifolia	*C. albicans*	200 mg/mL*	(Qader et al., 2013)
	C. dublicans	200 mg/mL*	
	C. glabrata	200 mg/mL*	
	C. krusei	200 mg/mL*	
	C. tropicalis	200 mg/mL*	
Ribes nigrum	*C. glabrata*	3.85 mg/mL	(Krisch et al., 2008)
	C. inconspicua	2.82 mg/mL	
	C. lipolytica	5.15 mg/mL	
	C. norvegica	3.62 mg/mL	
	C. parapsilosis	2.76 mg/mL	
	C. tropicalis	3.75 mg/mL	
	C. zeylanoides	1.83 mg/mL	
Rosmarinus officinalis	*C. albicans*	300 mg/mL*	(Abdul et al., 2012)
Salvia officinalis	*C. albicans*	15 mg/mL	(Jasim and Al-khaliq, 2011)
	C. parapsilosis	2.5 mg/mL	(Martins et al., 2015)
	C. tropicalis	1.25 mg/mL	(Martins et al., 2015)
Sapindus saponaria	*C. parapsilosis*	0.16 mg/mL	(Tsuzuki et al., 2007)
Scutellaria baicalensis	*C. albicans*	2.5 mg/mL 5 mg/mL	(Wong and Tsang, 2009)
Solanum nigrum	*C. albicans*	0.2 mg/mL	(Shamim et al., 2004)
	C. grabrata	1 mg/mL	
	C. tropicalis	0.2 mg/mL	
Solidago gigantean	*C. albicans*	0.8 mg/mL	(Webster et al., 2008)
	C. glabrata	0.1 mg/mL	
	C. krusei	0.8 mg/mL	
	C. lusitaniae	1.6 mg/mL	
	C. tropicalis	12.5 mg/mL	
Sonneratia alba	*C. albicans*	0.25 mg/mL	(Kaewpiboon et al., 2012)

Sonneratia caseolaris	*C. albicans*	0.125 mg/mL	(Kaewpiboon et al., 2012)
Syzygium aromaticum	*C. albicans* *C. glabrata* *C. krusei* *C. tropicalis*	0.782 mg/mL 0.025 mg/mL 0.098 mg/mL 0.003125 mg/mL	(Kim and Lee, 2012)
Thymus kotschyana	*C. albicanus* *C. glabrata* *C. krusei* *C. tropicalis*	200 mg/mL* 200 mg/mL* 200 mg/mL* 200 mg/mL*	(Qader et al., 2013)
Thymus vulgaris	*C. albicans*	300 mg/mL*	(Abdul et al., 2012)
Zingiber officinalis	*C. albicanus* *C. dublicans* *C. glabrata* *C. krusei* *C. tropicalis*	200 mg/mL* 200 mg/mL* 200 mg/mL* 200 mg/mL* 200 mg/mL*	(Qader et al., 2013)

*Concentration used to evaluate antifungal activity by disc diffusion. MIC - Minimum inhibitory concentration.

Table 3. Activity of ethanolic extracts against *Candida* species

Plant source	*Candida* species	MIC	References
Achillea biebersteinii	*C. albicans*	100 mg/mL	(Hassawi and Kharma, 2006)
Achillea fragantissima	*C. albicans*	150 mg/mL	(Hassawi and Kharma, 2006)
Acorus calamus	*C. albicans*	28.80 mg/mL	(Thirach et al., 2003)
Adiantum capillus veneris	*C. albicans*	1 mg/mL*	(Ishaq et al., 2014)
Allium cepa	*C. albicans*	10 mg/mL*	(Doddanna et al., 2013)
Allium sativum	*C. albicans*	1 mg/mL*	(Joe et al., 2009)
Allium sativum	*C. albicans* *C. grabrata* *C. tropicalis*	0.2 mg/mL 0.2 mg/mL 0.2 mg/mL	(Shamim et al., 2004)
Aloe barbadensis	*C. albicans* *C. grabrata* *C. tropicalis*	1 mg/mL 1 mg/mL 0.2 mg/mL	(Shamim et al., 2004)
Aloe excelsa	*C. albicans* *C. tropicalis*	1 mg/mL 0.2 mg/mL	(Coopoosamy and Magwa, 2007)
Aloe vera	*C. albicans*	10 mg/mL*	(Doddanna et al., 2013)
Andrographis paniculata	*C. albicans*	Viability: 103.85%	(Wong and Tsang, 2009)
Anthemis pseudocotula	*C. albicans*	150 mg/mL	(Hassawi and Kharma, 2006)
Artemisia herba-alba	*C. albicans*	100 mg/mL	(Hassawi and Kharma, 2006)
Ballota undulate	*C. albicans*	25 mg/mL	(Hashem, 2011)
Camellia sinensis	*C. albicans*	10 mg/mL*	(Doddanna et al., 2013)
Capparis spinosa	*C. albicans*	100 mg/mL*	(Mandeel and Taha, 2005)
Capsicum annum	*C. albicans*	17.5 mg/mL	(Ertürk, 2006)
Cassia alata	*C. albicans*	5.60 mg	(Timothy et al., 2012)
Cassia siamea	*C. albicans* *C. glabrata* *C. guilliermondii* *C. krusei* *C. parapsilosis* *C. tropicalis*	100 mg/mL 100 mg/mL 100 mg/mL 100 mg/mL 100 mg/mL 100 mg/mL	(Prabhakar et al., 2008)
Caulerpa scalpelliformis	*C. albicans* *C. glabrata* *C. guilliermondii* *C. krusei* *C. parapsilosis* *C. tropicalis*	100 mg/mL 100 mg/mL 100 mg/mL 100 mg/mL 100 mg/mL 100 mg/mL	(Prabhakar et al., 2008)

Cinnamomum sp.	*C. albicanus* *C. dublicans* *C. glabrata* *C. krusei* *C. tropicalis*	200 mg/mL* 200 mg/mL* 200 mg/mL* 200 mg/mL* 200 mg/mL*	(Qader et al., 2013)
Cleome amplyocarpa	*C. albicans*	75 mg/mL	(Hashem, 2011)
Colutea arborescens	*C. albicans*	12.5 mg/mL	(Ertürk, 2006)
Convolvulus arvensis	*C. albicans*	100 mg/mL*	(Mandeel and Taha, 2005)
Convolvulus arvensis	*C. albicans*	150 mg/mL	(Hassawi and Kharma, 2006)
Coscinium fenestratum	*C. albicans*	0.5 mg/mL	(Kaewpiboon et al., 2012)
Crataegus oxyacantha	*C. albicans*	10 mg/mL*	(Kostić et al., 2012)
Cressa cretica	*C. albicans*	100 mg/mL*	(Mandeel and Taha, 2005)
Cuminum cyminum	*C. albicans*	15 mg/mL	(Ertürk, 2006)
Cynara scolymus	*C. albicans* *C. lusitaniae*	12.5 mg/mL 12.5 mg/mL	(Zhu et al., 2005)
Dianthus coryophyllum	*C. albicans*	20 mg/mL	(Ertürk, 2006)
Emex spinosa	*C. albicans*	100 mg/mL*	(Mandeel and Taha, 2005)
Erica arborea	*C. albicans*	2.5 mg/mL	(Ertürk, 2006)
Eugenia caryophyllus	*C. albicans*	17.41 mg/mL	(Thirach et al., 2003)
Eugenia uniflora	*C. krusei*	0.25 mg/mL	(Correa-Royero et al., 2010)
Fagonia indica	*C. albicans*	100 mg/mL*	(Mandeel and Taha, 2005)
Fraxinus rhynchophylla	*C. albicans*	Viability: 77.56%	(Wong and Tsang, 2009)
Funtumia elastica	*C. albicans*	100 mg/mL*	(Adekunle and Ikumapayi, 2006)
Glycyrrhiza glabra	*C. albicans* *C. krusei* *C. nerformans* *C. pseudotropicalis*	1 mg/mL 2 mg/mL 0.5 mg/mL 1 mg/mL	(Fatima et al., 2009)
Heliotropium curassavicum	*C. albicans*	100 mg/mL*	(Mandeel and Taha, 2005)
Illicium verum	*C. albicans*	16 mg/mL	(Yazdani et al., 2009)
Isatis indigotica	*C. albicans*	Viability: 94.05%	(Wong and Tsang, 2009)
Juniperus oxycedrus	*C. albicans*	5 mg/mL	(Ertürk, 2006)
Lantana fucata	*C. krusei*	0.5 mg/mL	(Correa-Royero et al., 2010)
Laurus nobilis	*C. albicans*	5 mg/mL	(Ertürk, 2006)
Mahonia aquifolium	*C. tropicalis*	1000 µg/mL	(Volleková et al.,

			2003)
Mallotus oppositifolius	*C. albicans*	100 mg/mL*	(Adekunle and Ikumapayi, 2006)
Melissa officinalis	*C. albicans*	25 mg/mL	(Ertürk, 2006)
Mentha piperita	*C. albicans*	5 mg/mL	(Ertürk, 2006)
Mentha piperita	*C. albicans*	10 mg/mL*	(Doddanna et al., 2013)
Morinda morindoides	*C. albicans*	31.25 mg/mL	(Touré et al., 2011)
Morinda royoc	*C. krusei*	0.25 mg/mL	(Correa-Royero et al., 2010)
Murraya koenigii	*C. albicans*	10 mg/mL*	(Doddanna et al., 2013)
Myrcia cucullata	*C. krusei*	0.03125 mg/mL	(Correa-Royero et al., 2010)
Odina wodier	*C. albicans* *C. glabrata* *C. guilliermondii* *C. krusei* *C. parapsilosis* *C. tropicalis*	500 mg/mL 500 mg/mL 500 mg/mL 500 mg/mL 500 mg/mL 500 mg/mL	(Prabhakar et al., 2008)
Origanum vulgare	*C. albicans*	5 mg/mL 10 mg/mL	(Ličina et al., 2013)
Paullinia cupana	*C. albicans*	0.5 mg/mL	(Basile et al., 2013)
Pimpinella anisum	*C. albicans* *C. krusei* *C. parapsilosis* *C. pseudotropicalis* *C. tropicalis*	19 %, v/v 20 %, v/v 18 %, v/v 17 %, v/v 18 %, v/v	(Kosalec et al., 2005)
Piper nigrum	*C. albicans*	12.5 mg/mL	(Ertürk, 2006)
		1.5 mg/mL*	(Joe et al., 2009)
Piper regnellii	*C. albicans* *C. krusei* *C. parapsilosis*	0.125 mg/mL 0.5 mg/mL 0.5 mg/mL	(Pessini et al., 2005)
Plantago lanceolata (France)	*C. albicans*	200 mg/mL	(Hassawi and Kharma, 2006)
Plantago media	*C. albicanus* *C. dublicans* *C. glabrata* *C. krusei* *C. tropicalis*	200 mg/mL* 200 mg/mL* 200 mg/mL* 200 mg/mL* 200 mg/mL*	(Qader et al., 2013)
Pluchea ovalis	*C. albicans*	100 mg/mL*	(Mandeel and Taha, 2005)
Punica granatum	*C. albicans* *C. dubliniensis* *C. glabrata* *C. guilliermondii* *C. krusei*	0.25 mg/mL 0.25 mg/mL 0.25 mg/mL 0.125 mg/mL 0.125 mg/mL	(Anibal et al., 2013)

	C. lusitaniae	0.125 mg/mL	
	C. parapsilosis	0.125 mg/mL	
	C. rugosa	0.125 mg/mL	
	C. tropicalis	0.25 mg/mL	
	C. utilis	0.25 mg/mL	
Punica granatum	*C. albicanus*	200 mg/mL*	(Qader et al., 2013)
	C. dublicans	200 mg/mL*	
	C. glabrata	200 mg/mL*	
	C. krusei	200 mg/mL*	
	C. tropicalis	200 mg/mL*	
Quercus infectoria	*C. albicanus*	200 mg/mL*	(Qader et al., 2013)
	C. dublicans	200 mg/mL*	
	C. glabrata	200 mg/mL*	
	C. krusei	200 mg/mL*	
	C. tropicalis	200 mg/mL*	
Rhus angustifolia	*C. albicanus*	200 mg/mL*	(Qader et al., 2013)
	C. dublicans	200 mg/mL*	
	C. glabrata	200 mg/mL*	
	C. krusei	200 mg/mL*	
	C. tropicalis	200 mg/mL*	
Rhus coriaria	*C. albicans*	15 mg/mL	(Ertürk, 2006)
Sargassum wightii	*C. albicans*	100 mg/mL	(Prabhakar et al., 2008)
	C. glabrata	100 mg/mL	
	C. guilliermondii	100 mg/mL	
	C. krusei	100 mg/mL	
	C. parapsilosis	100 mg/mL	
	C. tropicalis	100 mg/mL	
Sclerocarya birrea	*C. parapsilosis*	0.21 mg/mL	(Masoko et al., 2008)
Solanum nigrum	*C. albicans*	0.2 mg/mL	(Shamim et al., 2004)
	C. grabrata	1 mg/mL	
	C. tropicalis	0.2 mg/mL	
Syzygium jambolanum	*C. albicans*	100 mg/mL	(Prabhakar et al., 2008)
	C. glabrata	100 mg/mL	
	C. guilliermondii	100 mg/mL	
	C. krusei	100 mg/mL	
	C. parapsilosis	100 mg/mL	
	C. tropicalis	100 mg/mL	
Tamarix arabica	*C. albicans*	100 mg/mL*	(Mandeel and Taha, 2005)
Thymus kotschyana	*C. albicanus*	200 mg/mL*	(Qader et al., 2013)
	C. dublicans	200 mg/mL*	
	C. glabrata	200 mg/mL*	
	C. krusei	200 mg/mL*	
	C. tropicalis	200 mg/mL*	
Zingiber officinale	*C. albicans*	1 mg/mL*	(Joe et al., 2009)
Zingiber officinalis	*C. albicanus*	200 mg/mL*	(Qader et al., 2013)
	C. dublicans	200 mg/mL*	

	C. glabrata	200 mg/mL*	
	C. krusei	200 mg/mL*	
	C. tropicalis	200 mg/mL*	

*Concentration used to evaluate antifungal activity by disc diffusion. MIC - Minimum inhibitory concentration.

Table 4. Activity of methanol-dichloromethane extracts against *Candida* species

Plant source	Species	MIC	References
Aframomum citratum	*C. albicans*	3.12 mg/mL	(Dzoyem et al., 2014)
	C. glabrata	4.68 mg/mL	
	C. guilliermondii	3.12 mg/mL	
	C. krusei	0.39 mg/mL	
	C. lusitaniae	0.78 mg/mL	
	C. parapsilosis	6.25 mg/mL	
	C. tropicalis	6.25 mg/mL	
Aframomum melegueta	*C. albicans*	6.25 mg/mL	(Dzoyem et al., 2014)
	C. guilliermondii	1.56 mg/mL	
	C. krusei	6.25 mg/mL	
	C. lusitaniae	3.12 mg/mL	
	C. parapsilosis	6.25 mg/mL	
	C. tropicalis	1.56 mg/mL	
Andrographis paniculata[*]	*C. albicans*	0.1 mg/mL	(Sule et al., 2012)
	C. krusei	0.25 mg/mL	
	C. tropicalis	0.1 mg/mL	
Bielschmiedia cinnamomea	*C. albicans*	3.12 mg/mL	(Dzoyem et al., 2014)
	C. glabrata	6.25 mg/mL	
	C. guilliermondii	6.25 mg/mL	
	C. lusitaniae	3.12 mg/mL	
	C. tropicalis	3.12 mg/mL	
Cinnamomum zeylanicum	*C. albicans*	3.12 mg/mL	(Dzoyem et al., 2014)
	C. glabrata	3.12 mg/mL	
	C. guilliermondii	0.78 mg/mL	
	C. krusei	0.78 mg/mL	
	C. lusitaniae	0.78 mg/mL	
	C. parapsilosis	3.12 mg/mL	
	C. tropicalis	0.097 mg/mL	
Dichrostachys glomerata	*C. albicans*	0.39 mg/mL	(Dzoyem et al., 2014)
	C. glabrata	3.12 mg/mL	
	C. guilliermondii	3.12 mg/mL	
	C. krusei	3.12 mg/mL	
	C. lusitaniae	0.39 mg/mL	
	C. parapsilosis	6.25 mg/mL	
	C. tropicalis	3.12 mg/mL	
Diospyros crassiflora	*C. albicans*	12.5 mg/mL	(Dzoyem et al., 2007)
	C. glabrata	25 mg/mL	
	C. krusei	12.5 mg/mL	
	C. tropicalis	12.5 mg/mL	
Dorstenia psilirus	*C. albicans*	0.39 mg/mL	(Dzoyem et al., 2014)
	C. glabrata	3.12 mg/mL	
	C. guilliermondii	1.56 mg/mL	
	C. krusei	3.12 mg/mL	
	C. lusitaniae	3.12 mg/mL	
	C. parapsilosis	3.12 mg/mL	
	C. tropicalis	0.39 mg/mL	

Echinops giganteus	*C. albicans* *C. glabrata* *C. guilliermondii* *C. lusitaniae* *C. parapsilosis* *C. tropicalis*	6.25 mg/mL 1.56 mg/mL 3.12 mg/mL 6.25 mg/mL 6.25 mg/mL 6.25 mg/mL	(Dzoyem et al., 2014)
Fagara leprieurii	*C. albicans* *C. glabrata* *C. krusei* *C. parapsilosis* *C. tropicalis*	3.12 mg/mL 3.12 mg/mL 6.25 mg/mL 6.25 mg/mL 6.25 mg/mL	(Dzoyem et al., 2014)
Fagara macrophylla	*C. albicans* *C. glabrata* *C. guilliermondii* *C. krusei* *C. lusitaniae* *C. tropicalis*	3.12 mg/mL 3.12 mg/mL 1.56 mg/mL 6.25 mg/mL 1.56 mg/mL 0.39 mg/mL	(Dzoyem et al., 2014)
Gonzalagunia rosea[*]	*C. albicans*	2.50 mg/mL	(Niño et al., 2007)
Imperata cylindrical	*C. albicans* *C. glabrata* *C. guilliermondii* *C. krusei* *C. lusitaniae* *C. parapsilosis* *C. tropicalis*	6.25 mg/mL 3.12 mg/mL 3.12 mg/mL 1.56 mg/mL 3.12 mg/mL 6.25 mg/mL 3.12 mg/mL	(Dzoyem et al., 2014)
Liabum asclepiadeum[*]	*C. albicans*	0.62 mg/mL	(Niño et al., 2007)
Mondia whitei	*C. albicans* *C. guilliermondii* *C. lusitaniae* *C. tropicalis*	3.12 mg/mL 6.25 mg/mL 3.12 mg/mL 3.12 mg/mL	(Dzoyem et al., 2014)
Monodora myristica	*C. albicans* *C. guilliermondii* *C. krusei* *C. lusitaniae* *C. tropicalis*	6.25 mg/mL 3.12 mg/mL 6.25 mg/mL 3.12 mg/mL 3.12 mg/mL	(Dzoyem et al., 2014)
Montanoa[*]	*C. albicans*	1.25 mg/mL	(Niño et al., 2007)
Olax subscorpioidea	*C. albicans* *C. glabrata* *C. guilliermondii* *C. krusei* *C. lusitaniae* *C. parapsilosis* *C. tropicalis*	0.097 mg/mL 1.56 mg/mL 0.78 mg/mL 1.56 mg/mL 0.19 mg/mL 0.39 mg/mL 0.048 mg/mL	(Dzoyem et al., 2014)
Pentadiplandra brazzeana	*C. albicans* *C. glabrata* *C. guilliermondii*	3.12 mg/mL 6.25 mg/mL 6.25 mg/mL	(Dzoyem et al., 2014)

	C. lusitaniae	6.25 mg/mL	
	C. tropicalis	1.56 mg/mL	
Piper capense	*C. albicans*	3.12 mg/mL	(Dzoyem et al., 2014)
	C. guilliermondii	3.12 mg/mL	
	C. krusei	3.12 mg/mL	
	C. lusitaniae	1.56 mg/mL	
	C. parapsilosis	3.12 mg/mL	
	C. tropicalis	0.19 mg/mL	
Piper guineense	*C. albicans*	3.12 mg/mL	(Dzoyem et al., 2014)
	C. glabrata	3.12 mg/mL	
	C. lusitaniae	1.56 mg/mL	
	C. parapsilosis	6.25 mg/mL	
	C. tropicalis	3.12 mg/mL	
Schizozygia caffaeoides[*]	*C. albicans*	2.5 mg/mL	(Kariba et al., 2001)
Scorodophloeus zenkeri	*C. albicans*	2.34 mg/mL	(Dzoyem et al., 2014)
	C. glabrata	4.68 mg/mL	
	C. guilliermondii	6.25 mg/mL	
	C. krusei	3.90 mg/mL	
	C. lusitaniae	2.34 mg/mL	
	C. parapsilosis	6.25 mg/mL	
	C. tropicalis	4.68 mg/mL	
Solanum melongena	*C. guilliermondii*	6.25 mg/mL	(Dzoyem et al., 2014)
	C. tropicalis	3.12 mg/mL	
Tetrapleura tretraptera	*C. albicans*	3.12 mg/mL	(Dzoyem et al., 2014)
	C. glabrata	6.25 mg/mL	
	C. guilliermondii	3.12 mg/mL	
	C. krusei	6.25 mg/mL	
	C. lusitaniae	3.12 mg/mL	
	C. parapsilosis	3.12 mg/mL	
	C. tropicalis	6.25 mg/mL	
Xylopia aethiopica	*C. albicans*	3.12 mg/mL	(Dzoyem et al., 2014)
	C. krusei	3.12 mg/Ml	
	C. parapsilosis	3.12 mg/mL	
	C. tropicalis	3.12 mg/mL	
Xylopia parviflora	*C. albicans*	6.25 mg/mL	(Dzoyem et al., 2014)
	C. glabrata	6.25 mg/mL	
	C. guilliermondii	3.12 mg/mL	
	C. krusei	3.12 mg/mL	
	C. lusitaniae	1.56 mg/mL	
	C. parapsilosis	3.12 mg/mL	
	C. tropicalis	3.12 mg/mL	

[*]Dichloromethane extracts. MIC - Minimum inhibitory concentration.

Table 5. Activity of methanolic extracts against *Candida* species

Plant sources	***Candida* species**	**MIC**	**References**
Adiantum capillus veneris	*C. albicans*	1 mg/mL*	(Ishaq et al., 2014)
Anagyris foetida	*C. albicans* *C. glabrata* *C. krusei*	12.5 mg/mL 25 mg/mL 12.5 mg/mL	(Darwish and Aburjai, 2011)
Andrographis paniculata	*C. albicans* *C. krusei* *C. tropicalis*	0.2 mg/mL 0.2 mg/mL 0.150 mg/mL	(Sule et al., 2012)
Arrabidaea chica	*C. albicans*	0.5 mg/mL	(Höfling et al., 2011)
Artemisia herba-alba	*C. albicans* *C. glabrata* *C. krusei*	6.3 mg/mL 25 mg/mL 12.5 mg/mL	(Darwish and Aburjai, 2011)
Caesalpinia pulcherrima	*C. albicans*	0.125 mg/disc*	(Parekh and Chanda, 2008)
Capparis spinosa	*C. albicans* *C. glabrata* *C. krusei*	12.5 mg/mL 12.5 mg/mL 12.5 mg/mL	(Darwish and Aburjai, 2011)
Cassia fistula	*C. albicans* *C. glabrata* *C. tropicalis*	0.150 mg/mL 0.1 mg/mL 0.250 mg/mL	(Irshad et al., 2011)
Centaurium erythraea	*C. albicans*	0.1 mg/mL	(Siler et al., 2014)
Centaurium littorale spp. *uliginosum*	*C. albicans*	0.2 mg/mL	(Siler et al., 2014)
Centaurium pulchellum	*C. albicans*	0.4 mg/mL	(Siler et al., 2014)
Centaurium spicatum	*C. albicans*	0.2 mg/mL	(Siler et al., 2014)
Centaurium tenuiflorum	*C. albicans*	0.2 mg/mL	(Siler et al., 2014)
Crossandra infundibuliformis	*C. krusei*	125 mg/mL	(Madhumitha and Saral, 2011)
Diospyros canaliculata	*C. albicans* *C. kefyr* *C. parapsilosis*	0.0125 mg/mL 0.025 mg/mL 0.0125 mg/mL	(Dzoyem et al., 2011)
Dorstenia turbinata	*C. albicans* *C. glabrata*	0.039 mg/mL 0.039 mg/mL	(Ngameni et al., 2009)
Ephedra pachyclada	*C. albicans*	0.0005 mg/mL*	(Parsaeimehr et al., 2010)
Ephedra procera	*C. albicans*	0.0005 mg/mL*	(Parsaeimehr et

			al., 2010)
Ephedra strobilacea	*C. albicans*	0.001 mg/mL*	(Parsaeimehr et al., 2010)
Equinops polyceras	*C. albicans* *C. glabrata* *C. krusei*	6.3 mg/mL 12.5 mg/mL 3.1 mg/mL	(Darwish and Aburjai, 2011)
Eucalyptus intertexta	*C. albicans*	0.0625 mg/mL	(Safaei-Ghomi and Ahd, 2010)
Eucalyptus largiflorens	*C. albicans*	0.0312 mg/mL	(Safaei-Ghomi and Ahd, 2010)
Eucalyptus sideroxylon	*C. albicans*	400 mg/mL*	(Ashour, 2008)
Eucalyptus torquata	*C. albicans*	400 mg/mL*	(Ashour, 2008)
Euphorbia hirta	*C. albicans*	3.13 mg/mL	(Rajeh et al., 2010)
Euphorbia macroclada	*C. albicans* *C. glabrata* *C. krusei*	12.5 mg/mL 25 mg/mL 12.5 mg/mL 25 mg/mL 12.5 mg/mL 25 mg/mL	(Darwish and Aburjai, 2011)
Euphorbia tirucalli	*C. albicans*	0.125 mg/disc*	(Parekh and Chanda, 2008)
Glycyrrhiza glabra	*C. albicans*	0.0005 mg/mL*	(Karomi et al., 2012)
Gonzalagunia rosea	*C. albicans*	1.25 mg/mL	(Niño et al., 2007)
Holarrhena antidysenterica	*C. tropicalis*	0.125 mg/disc*	(Parekh and Chanda, 2008)
Hybiscus sabdariffa	*C. krusei*	25 mg/mL	(Darwish and Aburjai, 2011)
Hypericum trequetrifolium	*C. albicans* *C. glabrata* *C. krusei*	12.5 mg/mL 25 mg/mL 12.5 mg/mL	(Darwish and Aburjai, 2011)
Hyssopus officinalis subsp. *pilifer*	*C. albicans*	10 mg/mL	(Džamić et al., 2013)
Laurus nobilis	*C. albicans* *C. glabrata* *C. holmii* *C. insane* *C. krusei* *C. tropicalis*	0.13 mg/mL 0.13 mg/mL 0.16 mg/mL 0.07 mg/mL 0.07 mg/mL 0.04 mg/mL	(Unver et al., 2008)
Leiothrix spiralis	*C. albicans* *C. krusei* *C. parapsilosis* *C. tropicalis*	0.5 mg/mL 0.5 mg/mL 0.25 mg/mL 1 mg/mL	(Araújo et al., 2012)
Lepidium sativum	*C. albicans*	25 mg/mL	(Darwish and Aburjai, 2011)

Mangifera indica	*C. albicans*	0.125 mg/disc*	(Parekh and Chanda, 2008)
Mentha longifolia	*C. albicans* *C. glabrata* *C. krusei*	6.3 mg/mL 12.5 mg/mL 12.5 mg/mL	(Darwish and Aburjai, 2011)
Mesua ferra	*C. albicans*	0.125 mg/disc*	(Parekh and Chanda, 2008)
Mindium laevigatum	*C. albicans*	0.1 mg/mL	(Modaressi et al., 2013)
Montanoa	*C. albicans*	0.62 mg/mL	(Niño et al., 2007)
Munnozia senecionidis	*C. albicans*	2.5 mg/mL	(Niño et al., 2007)
Origanum syriacum	*C. albicans* *C. glabrata* *C. krusei*	6.3 mg/mL 12.5 mg/mL 12.5 mg/mL	(Darwish and Aburjai, 2011)
Paeonia rockii	*C. albicans*	0.025 mg/mL	(Picerno et al., 2011)
Phlomis brachydon	*C. albicans* *C. glabrata* *C. krusei*	6.3 mg/mL 12.5 mg/mL 3.1 mg/mL	(Darwish and Aburjai, 2011)
Pimpinella anisum	*C. albicans* *C. glabrata* *C. krusei*	12.5 mg/mL 12.5 mg/mL 25 mg/mL	(Darwish and Aburjai, 2011)
Pimpinella anisum	*C. albicans*	16 mg/mL	(Yazdani et al., 2009)
Psidium sartorianum	*C. albicans*	16 mg/mL	(Camacho-Hernández et al., 2004)
Ribes x nidigrolaria	*C. glabrata* *C. inconspicua* *C. lipolytica* *C. norvegica* *C. parapsilosis* *C. tropicalis* *C. zeylanoides*	2.91 mg/mL 3.33 mg/mL 4.67 mg/mL 10.98 mg/mL 3.56 mg/mL 4.23 mg/mL 5.68 mg/mL	(Krisch et al., 2008)
Ribes nigrum	*C. guilliermondii* *C. inconspicua* *C. parapsilosis* *C. tropicalis*	6.13 mg/mL 4.22 mg/mL 4.41 mg/mL 7.16 mg/mL	(Krisch et al., 2008)
Ribes uva-crispa	*C. glabrata* *C. lipolytica*	4.60 mg/mL 4.63 mg/mL	(Krisch et al., 2008)
Salvia officinalis	*C. clus* *C. tropicalis*	0.16 mg/mL 0.16 mg/mL	(Unver et al., 2008)
Saussurea lappa	*C. albicans*	0.125 mg/disc*	(Parekh and Chanda, 2008)
Schistocarpha sinforosi	*C. albicans*	2.5 mg/mL	(Niño et al.,

			2007)
Schizozygia caffaeoides	*C. albicans*	10 mg/mL	(Kariba et al., 2001)
Sclerocarya birrea	*C. parapsilosis*	0.32 mg/mL	(Masoko et al., 2008)
Thea sinensis	*C. albicans* *C. glabrata* *C. krusei*	6.3 mg/mL 12.5 mg/mL 12.5 mg/mL	(Darwish and Aburjai, 2011)
Thecacoris annobonae	*C. albicans*	0.3125 mg/mL	(Kuete et al., 2010)
Thymbra spicata	*C. albicans* *C. clus* *C. glabrata* *C. krusei* *C. parapsilosis* *C. tropicalis*	0.04 mg/mL 0.01 mg/mL 0.01 mg/mL 0.01 mg/mL 0.01 mg/mL 0.01 mg/mL	(Unver et al., 2008)
Trapa natans	*C. tropicalis*	0.125 mg/disc*	(Parekh and Chanda, 2008)
Trigonella foenum-graecum	*C. albicans* *C. krusei*	12.5 mg/mL 12.5 mg/mL	(Darwish and Aburjai, 2011)
Varthemia iphionoides	*C. albicans*	6.3 mg/mL	(Darwish and Aburjai, 2011)
Verbesina nudipes	*C. albicans*	2.5 mg/mL	(Niño et al., 2007)
Vitex negundo	*C. albicans*	0.125 mg/disc*	(Parekh and Chanda, 2008)

*Concentration used to evaluate antifungal activity by disc diffusion. MIC - Minimum inhibitory concentration.

Table 6. Activity of hydroalcoholic extracts against *Candida* species

	Plant source	***Candida* species**	**MIC**	**References**
Ethanol: water (90:10 v/v)	*Sapindus saponaria*	*C. parapsilosis*	0.4 mg/mL	(Tsuzuki et al., 2007)
Ethanol: water (70:30 v/v)	*Emblica officinalis*	*C. albicans*	0.1024 mg/mL	(Tharkar et al., 2010)
Ethanol: water (70:30 v/v)	*Glycyrrhiza glabra*	*C. albicans*	0.512 mg/mL	(Tharkar et al., 2010)
Ethanol: water (70:30 v/v)	*Momordica charantia*	*C. guilhermondii*	0.1 mg/mL*	(Silva, 2012)
Ethanol: water (70:30 v/v)	*Punica granatum*	*C. albicans*	0.1 mg/mL*	(Silva, 2012)
		C. guilhermondii	0.1 mg/mL*	
		C. krusei	0.1 mg/mL*	
		C. parapsilosis	0.1 mg/mL*	
		C. tropicalis	0.1 mg/mL*	
Ethanol: water (70:30 v/v)	*Syzygium aromaticum*	*C. guilhermondii*	0.05 mg/mL	(Silva, 2012)
		C. parapsilosis	0.1 mg/mL*	
		C. tropicalis	0.1 mg/mL*	
Ethanol: water (50:50 v/v)	*Achyranthes aspera*	*C. albicans*	0.3 mg/mL	(Mathur et al., 2011)
Ethanol: water (50:50 v/v)	*Punica granatum*	*C. albicans*	0.0039 mg/mL	(Endo et al., 2010)
		C. parapsilosis	0.0039 mg/mL	
Methanol: water (90:10 v/v)	*Cassia fistula*	*C. albicans*	0.025 mg/mL	(Bhalodia et al., 2012)
Methanol: water (80:20 v/v)	*Castanea sativa*	*C. albicans*	0.625 mg/mL	(Barros et al., 2013a)
		C. tropicalis	0.625 mg/mL	
Methanol: water (80:20 v/v)	*Cistus lanadifer*	*C. tropicalis*	0.625 mg/mL	(Barros et al., 2013b)
Methanol: water (80:20 v/v)	*Filipendula ulmaria*	*C. albicans*	0.625 mg/mL	(Barros et al., 2013a)
		C. tropicalis	0.155 mg/mL	
Methanol: water (80:20 v/v)	*Rosa micrantha*	*C. albicans*	0.05 mg/mL	(Barros et al., 2013a)

		C. tropicalis	0.155 mg/mL	
Methanol: water (80:20 v/v)	*Salvia officinalis*	*C. parapsilosis*	2.5 mg/mL	(Martins et al., 2015)
		C. tropicalis	1.25 mg/mL	

*Concentration used to evaluate antifungal activity by disc diffusion. MIC - Minimum inhibitory concentration.

Table 7. Activity of other extracts against *Candida* species

Extract	Plant source	*Candida* species	MIC	References
Dimethyl sulfoxide (DMSO)	*Eleutherine plicata*	*C. albicans*	259 mg/mL	(Menezes et al., 2009)
	Psidium guajava		125 mg/mL	
	Syzygium aromaticum		62.5 mg/mL	
Diethyl ether	*Origanum vulgare*	*C. albicans*	5 mg/mL	(Ličina et al., 2013)
Ethyl acetate	*Crossandra infundibuliformis*	*C. krusei*	125 mg/mL	(Madhumitha and Saral, 2011)
	Curcuma zedoaria	*C. albicans*	12.5 mg/mL	(Zhu et al., 2005)
		C. lusitaniae	12.5 mg/mL	
	Hyssopus officinalis subsp. *Pilifer*	*C. albicans*	7.00 mg/mL	(Džamić et al., 2013)
	Origanum vulgare	*C. albicans*	5 mg/mL	(Ličina et al., 2013)
Tinctures	*Anacardium occidentale*	*C. albicans*	100 mg/mL	(Cardoso et al., 2012)
		C. krusei	100 mg/mL	
	Malva sylvestris	*C. albicans*	100 mg/mL	(Cardoso et al., 2012)
		C. krusei	25 mg/mL	
		C. tropicalis	100 mg/mL	
	Salvia officinalis	*C. krusei*	100 mg/mL	(Cardoso et al., 2012)

MIC - Minimum inhibitory concentration.

Table 8. Activity of phenolics acids against *Candida* species

Phenolic acids	Source	*Candida* species	MIC	References
Hydroxycinnamic acid derivatives				
Caffeic acid	Commercial compound	*C. albicans* *C. parapsilosis*	8 µg/mL 16 µg/mL	(Ozçelik et al., 2011)
Chlorogenic acid	Commercial compound	*C. albicans* *C. parapsilosis*	8 µg/mL 16 µg/mL	(Ozçelik et al., 2011)
m-coumaric acid (2-hydroxycinnamic acid)	Commercial compound	*C. albicans; C. parapsilosis*; *C. glabrata*; *C. tropicalis; C. krusei*; *C. lusitaniae*	820 µg/mL[a]	(Faria et al., 2011)
o-coumaric acid (3-hydroxycinnamic acid)	Commercial compound	*C. albicans; C. parapsilosis;* *C. glabrata; C. tropicalis; C. krusei*; *C. lusitaniae*	820 µg/mL[a]	(Faria et al., 2011)
p-coumaric acid (4-hydroxycinnamic acid)	Commercial compound	*C. albicans*	40 µg/mL	(Siler et al., 2014)
		C. albicans; C. parapsilosis; C. glabrata; *C. tropicalis; C. krusei*; *C. lusitaniae*	820 µg/mL[a]	(Faria et al., 2011)
Ferulic acid	Commercial compound	*C. albicans*	20 µg/mL	(Siler et al., 2014)
4-hydroxy-3-methoxy cinnamic acid	*Halimodendron halodendron*	*C. albicans*	200 µg/mL	(Wang et al., 2012)
Hydroxybenzoic acid derivatives				
Gallic acid	*Lythrum*	*C. albicans*	2500 µg/mL	(Manayi et

	salicaria			al., 2013)
	Paeonia rockii	*C. albicans*	30 µg/mL	(Picerno et al., 2011)
	Pelargonium reniforme subsp. *reniforme*	*C. albicans* *C. glabrata* *C. krusei*	500 µg/mL 62 µg/mL 125 µg/mL	(Latte and Kolodziej, 2000)
	Commercial compound	*C. albicans* *C. parapsilosis*	8 µg/mL 16 µg/mL	(Ozçelik et al., 2011)
Gentisic acid	*Stenoloma chusanum*	*C. albicans*	50 µg/mL	(Ren et al., 2009)
2-*O*-β-D-(6-*O*-gentisoylglucosyl)gentisic acid	*Stenoloma chusanum*	*C. albicans*	100 µg/mL	(Ren et al., 2009)
p-Hydroxybenzoic acid	*Halimodendron halodendron*	*C. albicans*	100 µg/mL	(Wang et al., 2012)
Salicylic acid	*Halimodendron halodendron*	*C. albicans*	150 µg/mL	(Wang et al., 2012)
	Commercial compound	*C. albicans; C. parapsilosis; C. glabrata; C. tropicalis* *C. krusei; C. lusitaniae*	690 µg/mL[a]	(Faria et al., 2011)
Syringic acid	*Stenoloma chusanum*	*C. albicans*	50 µg/mL	(Ren et al., 2009)
Vanillic acid	*Stenoloma chusanum*	*C. albicans*	50 µg/mL	(Ren et al., 2009)
4-*O*-β -D-(6-*O*-gentisoylglucosyl) vanillic acid	*Stenoloma chusanum*	*C. albicans*	50 µg/mL	(Ren et al., 2009)
4-Acetoxy vanillic acid	*Thecacoris annobonae*	*C. albicans*	156.25 µg/mL	(Kuete et al., 2010)

Other phenolic acids/related compounds				
Albicanyl caffeate	Commercial compound	*C. albicans*	4 µg/mL	(Sun et al., 2004)
Dihydro-N-caffeoyltyramine[b]	*Lycium chinense*	*C. albicans*	5 µg/mL	(Lee et al., 2004)
cis-N-caffeoyltyramine[b]	*Lycium chinense*	*C. albicans*	40 µg/mL	(Lee et al., 2004)
trans-N-Feruloyloctopamine[b]	*Lycium chinense*	*C. albicans*	10 µg/mL	(Lee et al., 2004)
trans-N-Caffeoyltyramine[b]	*Lycium chinense*	*C. albicans*	5 µg/mL	(Lee et al., 2004)
3,3′,4′-tri-*O*-methylellagic acid-4-*O*-β-D-glucopyranoside	*Lythrum salicaria*	*C. albicans*	312 µg/mL	(Manayi et al., 2013)
Quinic acid	Commercial compound	*C. albicans* *C. parapsilosis*	8 µg/mL 16 µg/mL	(Ozçelik et al., 2011)

MIC - Minimum inhibitory concentration. [a]Tested concentration and not MIC. [b] Phenolic amides

Table 9. Activity of flavonoids against *Candida* species

Flavonoids	**Source**	***Candida* species**	**MIC**	**References**
Flavonols				
Kaempferol	*Origanum vulgare* subsp. *gracile; Origanum acutidens*	*C. albicans; C. glabrata*	0.1 µg/g[a] 0.5 µg/g[a]	(Kursat et al., 2011)
Morin	*Origanum vulgare* subsp. *gracile; Origanum acutidens*	*C. albicans; C. glabrata*	42.8 µg/g[a] 4.5 µg/g[a]	(Kursat et al., 2011)
Myricetin	*Origanum vulgare* subsp. *gracile; Origanum acutidens*	*C. albicans; C. glabrata*	0.2 µg/g[a] 1.2 µg/g[a]	(Kursat et al., 2011)
Quercetin	*Buddleja salviifolia*	*C. albicans*	125 µg/mL	(Pendota et al., 2013)
	Origanum vulgare subsp. *gracile*	*C. albicans; C. glabrata*	0.3 µg/g[a]	(Kursat et al., 2011)
	Halimodendron halodendron	*C. albicans*	250 µg/mL	(Wang et al., 2012)
	Commercial compound	*C. albicans; C. parapsilosis*	8 µg/mL	(Ozçelik et al., 2011)
3-*O*-methylquercetin	*Halimodendron halodendron*	*C. albicans*	200 µg/mL	(Wang et al., 2012)
3,3'-di-*O*-methylquercetin	*Halimodendron halodendron*	*C. albicans*	200 µg/mL	(Wang et al., 2012)

8-*O*-methylretusin	*Halimodendron halodendron*	*C. albicans*	250 µg/mL	(Wang et al., 2012)
8-*O*-methylretusin-7-*O*-β-D-glucopyranoside	*Halimodendron halodendron*	*C. albicans*	250 µg/mL	(Wang et al., 2012)
Rutin	*Origanum vulgare* subsp. *gracile*	*C. albicans; C. glabrata*	6.4 µg/g[a]	(Kursat et al., 2011)
	Commercial compound	*C. albicans*	40 µg/mL	(Siler et al., 2014)
Flavones				
Apigenin	Commercial compound	*C. albicans; C. parapsilosis*	8 µg/mL 16 µg/mL	(Ozçelik et al., 2011)
Luteolin-6-C-β-D-glucopyranoside	*Leiothrix spiralis*	*C. parapsilosis*	125 µg/mL	(Araújo et al., 2011)
4′-methoxyluteolin-6-C-β-D-glucopyranoside	*Leiothrix spiralis*	*C. albicans*	125 µg/mL	(Araújo et al., 2011)
3,5,7,8,4'-pentahydroxy-3'-methoxy flavone	*Halimodendron halodendron*	*C. albicans*	250 µg/mL	(Wang et al., 2012)
Flavanones				
Naringin	Commercial compound	*C. albicans* *C. parapsilosis*	8 µg/mL 16 µg/mL	(Ozçelik et al., 2011)
Naringenin	*Origanum acutidens*	*C. albicans; C. glabrata*	10.3 µg/g[a]	(Kursat et al., 2011)
Isoflavones				
Genistein	Commercial compound	*C. albicans; C. parapsilosis*	8 µg/mL	(Ozçelik et al., 2011)
2′-*O*-	*Mirabilis*	*C. albicans*	16-25 µg/mL	(Yang et

methylabronisoflavone	*jalapa*			al., 2001)
9-*O*-methyl-4-hydroxyboeravinone B	*Mirabilis jalapa*	*C. albicans*	48 µg/mL	(Yang et al., 2001)
Flavolignan				
Silibinin	Commercial compound	*C. albicans* *C. parapsilosis*	4 µg/mL 8 µg/mL	(Ozçelik et al., 2011)
Silymarin	Commercial compound	*C. albicans* *C. parapsilosis*	8 µg/mL 16 µg/mL	(Ozçelik et al., 2011)

MIC- Minimum inhibitory concentration. [a]Compound concentration in the tested extract.

Table 10. Activity of hydrolyzable tannins, stilbenes and xanthones against *Candida* species

Hydrolyzable tannins	**Source**	***Candida* species**	**MIC**	**References**
Corilagin	*Pelargonium reniforme* subsp. *reniforme*	*C. albicans* *C. glabrata* *C. krusei*	500 μg/mL 31 μg/mL 125 μg/mL	(Latte and Kolodziej, 2000)
Glucogallin	*Pelargonium reniforme* subsp. *reniforme*	*C. glabrata* *C. krusei*	31 μg/mL 125 μg/mL	(Latte and Kolodziej, 2000)
Methyl ester	*Pelargonium reniforme* subsp. *reniforme*	*C. glabrata* *C. krusei*	31 μg/mL 125 μg/mL	(Latte and Kolodziej, 2000)
Pelargoniin	*Pelargonium reniforme* subsp. *reniforme*	*C. albicans* *C. glabrata* *C. krusei*	500 μg/mL 31 μg/mL 125 μg/mL	(Latte and Kolodziej, 2000)
Phyllantusiin	*Pelargonium reniforme* subsp. *reniforme*	*C. albicans* *C. glabrata* *C. krusei*	500 μg/mL 31 μg/mL 125 μg/mL	(Latte and Kolodziej, 2000)
Punicalagin	*Punica granatum*	*C. albicans* *C. parapsilosis*	3.9 μg/mL 1.9 μg/mL	(Endo et al., 2010)
Not specified	*Rhizophora apiculate*	*C. albicans*	6250 μg/mL	(Lim et al., 2006)
Stilbenes				
Resveratrol	Commercial compound	*C. albicans*	16 μg/mL	(Sun et al., 2004)
		C. albicans	20 μg/mL	(Jung et al., 2005)
3,4'-difluorostilbene	Commercial compound	*C. albicans*	16 μg/mL	(Sun et al., 2004)
Xanthones				
8-carboxy-methyl-1,3,5,6-tetrahydroxyxanthone	*Leiothrix spiralis*	*C. albicans* *C. krusei* *C. parapsilosis* *C. tropicalis*	62.5 μg/mL 15.7 μg/mL 15.7 μg/mL 31.25 μg/mL	(Araújo et al., 2011)
Mangiferin	Commercial compound	*C. albicans*	40 μg/mL	(Siler et al., 2014)

MIC - Minimum inhibitory concentration.

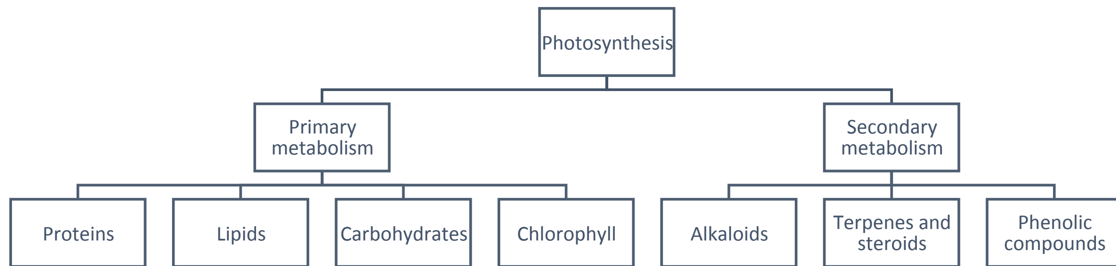
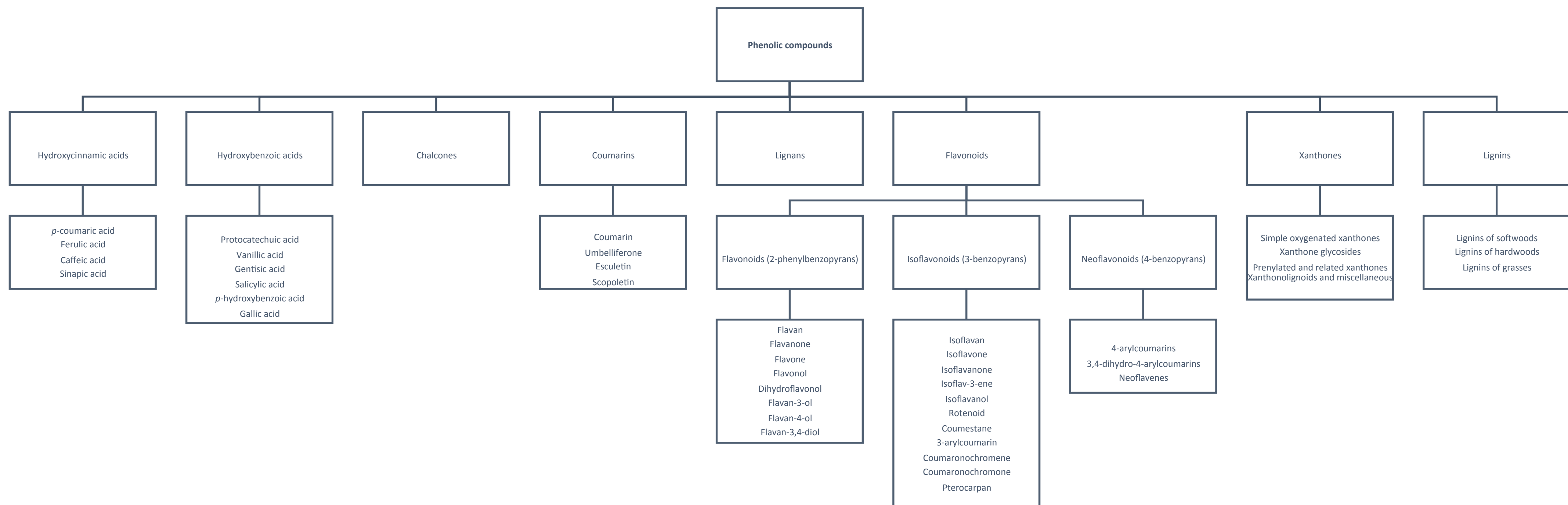


Figure 1: Relationship between the primary and secondary metabolism in plants.



Phenolic compounds
Hydroxycinnamic acids
Hydroxybenzoic acids
Chalcones
Coumarins
Lignans
Flavonoids
Xanthones
Lignins
p-coumaric acid
Ferulic acid
Caffeic acid
Sinapic acid
Protocatechuic acid
Vanillic acid
Gentisic acid
Salicylic acid
p-hydroxybenzoic acid
Gallic acid
Coumarin
Umbelliferone
Esculetin
Scopoletin
Flavonoids (2-phenylbenzopyrans)
Isoflavonoids (3-benzopyrans)
Neoflavonoids (4-benzopyrans)
Simple oxygenated xanthones
Xanthone glycosides
Prenylated and related xanthones
Xanthonolignoids and miscellaneous
Lignins of softwoods
Lignins of hardwoods
Lignins of grasses
Flavan
Flavanone
Flavone
Flavonol
Dihydroflavonol
Flavan-3-ol
Flavan-4-ol
Flavan-3,4-diol
Isoflavan
Isoflavone
Isoflavanone
Isoflav-3-ene
Isoflavanol
Rotenoid
Coumestane
3-arylcoumarin
Coumaronochromene
Coumaronochromone
Pterocarpan
4-arylcoumarins
3,4-dihydro-4-arylcoumarins
Neoflavenes