Plant Phenolics for Overcoming Multidrug Resistance in Human Fungal Pathogen

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Abstract

In spite of significant advances being made in the improvement of antifungal drugs, only limited number of drugs is currently available, and that too are not able to keep pace with the evolution of multidrug resistance (MDR). The urgent need includes the development of alternative drugs that are more efficient and tolerant than those traditionally already in use. Natural plant phenolics are among the most commonly occurring type of secondary metabolite in nature which is constantly being expanded through the discovery of new natural products. Interest in phenolics and the search for new biological activities within members of this class have intensified in recent years, as evidenced by the evaluation of their potential antifungal activities. Among most human pathogenic fungi, *Candida albicans* is of extreme importance due to their high frequency of colonization and infection in humans. Since nature has plethora of many promising natural compounds which can efficiently be exploited to improve the antifungal therapeutics, the objective of this book chapter is to describe the development of plant phenolics as antifungals for the treatment of *Candida* species and to note the most promising compounds with their diverse mechanism of actions and their uses in combination with traditional drugs.

Keywords

Candida · MDR · Natural phenolics · Efflux pumps · Cell membrane · Cell wall · Morphogenesis · Biofilm · Cell adherence

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17.1 Introduction

Fungal infections are the fourth most leading cause of hematogenous infections worldwide, which are mostly contributed by *Candida* genus (Pierce 2005). It consists of more than 150 species including the major *Candida albicans* and non-*albicans* species like *Candida auris*, *Candida tropicalis*, and *Candida glabrata*. Generally, *Candida* is a part of human microbiota where they normally reside in the body surfaces like oral cavity, gastrointestinal tract, and vagina, in a commensal manner, but under immunocompromised conditions, they turned out to be a great menace to human population (Kim and Sudbery 2011). The magnitude of fungal infections is increasing due to increment in number of transplants and hospitalized patients. The other factors contributing to the rise in infections are the prolonged usage of antifungal drugs and long chemotherapy treatments which result in the alarming problem of drug resistance by a phenomenon known as multidrug resistance (MDR) posing additional challenge for the health industries and researchers. The available few drugs belonging to classes azoles, polyenes, echinocandins, allylamines, and flucytosine are being resisted by the *Candida* species as been reported by number of case studies in hospitals. The problem of nosocomial infections is compounded due to the biofilm formation by *Candida* species, which resides in the indwelling devices like catheters used for the treatment of patients with another disease like AIDS or transplant patients. Hence, researches are now more focused on the search for the new drugs which could be used potentially against rising *Candida* infections.

Nowadays, plant-derived products are being favored over the synthetic products, due to their minimal side effects, cost-effectiveness, and potential. Plants are a rich source of secondary metabolites which they utilize for their defense against animals or microbes. These metabolites have been shown in various studies to possess many antimicrobial properties. Therefore, these secondary metabolites can be exploited for exploring the vast potential of these compounds that may be used as antifungal drugs. Secondary metabolites consist of diverse classes like terpenoids, alkaloids, phenolic compounds, alcohols, and acids. These classes consist of many potential compounds which are being employed for various uses due to their antimicrobial, antiseptic, anticancer, antioxidant, and anti-inflammatory properties (Ksouri et al. 2012). Among these, phenolic compounds comprise a major class of plant secondary metabolites being broadly distributed over more than 8000 phenolic structures currently identified. Previously, we have reviewed the antifungal action of phenolic compounds across various pathogenic fungi (Ansari et al. 2013). The present book chapter is written with the objective to summarize at a common platform the identification of diverse phenolic compounds as promising antifungals for the treatment of *Candida* species particularly with their probable mode of actions.

17.2 Classification of Phenolic Compounds

These compounds can contain one or more aromatic rings with at least one or more hydroxyl group species. Phenolic acids, flavonoids, and tannins are the most studied groups of phenolic compounds, comprising molecules with evidenced antifungal properties. The following sections will deal with few members of each classes.

17.2.1 Hydroxycinnamic Acids

They are the most commonly occurring phenolic compounds which belong to non-flavonoid polyphenols and are also known as hydroxycinnamates (Stalmach 2014). They are hydroxy metabolites of cinnamic acids which have benzene ring in which three-carbon chain is attached because of which they are included in phenylpropanoid group. They are synthesized by mevalonate-shikimate biosynthesis pathway in plants involving the phenylalanine and tyrosine as precursors (El-Seedi et al. 2012). The derivatives are also produced such as amides (combination with amino acids or peptides) and esters (combination with hydroxyl acids or glycosides). They are most commonly produced in fruits, cereals seeds, and vegetables. Their derivatives also play a role in acting as a precursor for the formation of lignans, anthocyanins, flavonoids, etc. They have important anti-inflammatory and antioxidant properties. The antioxidant nature of hydroxycinnamic acids has broad application in diverse fields like industrial additives or as health agents. They worked effectively against the oxidation-related diseases like inflammatory injury, cardiovascular diseases, atherosclerosis, and cancer. It has radical scavenging activity and chelation of transition metals or inhibition of reactive oxygen species (ROS) enzymes by modulation of gene expression (Teixeira et al. 2013). They are widely used as health beneficiary in various metabolic syndrome like anti-inflammatory agents, cardiovascular diseases, diabetes, and dyslipidemia (Alam et al. 2016). They also have antimicrobial, anti-collagenase, anti-melanogenic, and anti-tyrosinase activities. The pharmacological properties are contributed by presence of multiple hydroxyl groups in their chemical structure. The major hydrocinnamic acids are as follows.

17.2.2 Caffeic Acid

It is the major constituent and predominant among the other forms of hydroxycinnamic acid. It is around 75% of the total hydroxycinnamic acid in citrus fruits. The synthesis of caffeic acid is due to the hydroxylation of p-coumaric acid. It has medicinal properties, such as antitumor, antioxidant, antimicrobial, anti-inflammatory, and antidiabetic activities. They have role in decreasing the inflammation by lowering the expression of inflammatory mediator TNF-α (Alam et al. 2016). It has role in inhibiting the early stage of biofilm formation in *C. albicans*. The esters of caffeic acid have found to be effective against mature biofilm and more

potent in comparison with the known antifungal drug fluconazole (FLC) with lower minimum inhibitory concentration (MIC) values (De Vita et al. 2014). Caffeic acid phenethyl ester (CAPE) is the most studied derivative due to its potent antioxidant activity. It has also known to inhibit the clinical isolates of *Candida* by showing synergistic nature with known antifungal drug. The results have also shown that combination of FLC and CAPE has reduced the fungal burden and increased the longevity in nematode model, *Caenorhabditis elegans*. They have proved CAPE as promising therapeutics against resistant *C. albicans*. Another study by Sun et al. (2018) has demonstrated that CAPE shows synergism with the caspofungin and disrupts the iron homeostasis in *C. albicans*. CAPE performs this action by two ways: either by free radicals formation reactions or functional defects of mitochondrial respiratory chain CI and energy depletion in *C. albicans* [10]. Caffeic acids have been reported to inhibit the planktonic cells of *C. albicans* by targeting the glyoxylate cycle and inhibiting the activity of crucial enzyme called as isocitrate lyase (Cheah et al. 2014).

17.2.3 P-Coumaric Acid

It is one of the most dominant of all hydroxycinnamic acids. It is present in eggplants in very substantial amount, as well as broccoli and asparagus. It is synthesized by tyrosine and phenylalanine and is the major precursor in the further synthesis of other cinnamic acids. It has known antioxidant, antimicrobial, anti-inflammatory, antitumor, and antiplatelet aggregation properties. Due to their depigmenting potential and antioxidant nature, anti-collagenase, antimicrobial, and anti-inflammatory activities are being exploited to be used for cosmeceutical use. The methanolic extracts from various plants such as *Rosa rugosa*, *Ligusticum mutellina* L., *Limonium avei*, *Kitaibelia vitifolia*, and *Tamarix gallica* L. have been reported to inhibit the candidal growth and show varying MIC values (Teodoro et al. 2015a, b).

17.2.4 Ferulic Acid

It is the most common hydroxycinnamic acid which is present in plant cell walls and abundantly found in cereals as dietary source and corn bran, wheat bran, eggplant, artichokes, and beets. It is synthesized from caffeic acid by the enzyme caffeate O-methyltransferase. It has a variety of potential therapeutic effects which can be useful in the treatment of various diseases like cancer, diabetes, and lung and cardiovascular diseases. It has known antimicrobial and anti-inflammatory properties and neuroprotective and photoprotective effects. Ferulic acid has apoptotic effect on *C. albicans* and *C. glabrata*. The synergism of ferulic acid with caspofungin was found to be effective against the candidal infections. Their combinatorial action was fungicidal in nature as compared with the individual effect of ferulic acid and caspofungin. This compound has potential to be used for anticandidal treatment (Canturk 2018). The ferulic acid extracted from ethanolic

and aqueous extracts from various plants has been shown to inhibit the candidal growth. In a study by Panwar et al. (2016), ferulic acid-encapsulated chitosan nanoparticles have been found to be effective against the candidal biofilm residing in dwelling devices. This approach can be a promising alternative approach for the conventional therapeutic methods.

17.2.5 Sinapic Acid

It is a 3,5-dimethoxy-4-hydroxycinnamic acid found in citrus, berry fruits, vegetables, cereals, and oilseed crops (Chen 2016). It has known antioxidant, anti-inflammatory, antiglycemic, anticancer, and antibacterial activities. It has been reported in pathological conditions such as diabetes, inflammation, oxidative stress, and neurodegeneration (Zou et al. 2002). It can exist in free form or ester form such as sinapine (sinapoylcholine), sinapoyl esters, and sinapoyl malate. The sinapic acid derivatives such as 4-vinylsyringol, sinapine, and syringaldehyde have shown antioxidant activity, acetylcholinesterase inhibition, and antimutagenicity (Kuwahara et al. 2004). The sinapic acid derivative called as syringaldehyde has been studied for its antifungal potential against *Candida guilliermondii (*Kelly et al. 2008*)*.

17.2.6 Rosmarinic Acid

It is found in *Rosmarinus officinalis* L. and synthesized from esterification of both caffeic acid and 3,4-dihydroxyphenyllactic acid. It has known antioxidant, antitumor, anti-inflammatory, and antimicrobial properties. It has high radical-scavenging activity and medicinal properties which have been exploited in pharmaceutical and cosmetic sectors. It has been reported in a study by Calixto et al. (2015) that rosmarinic acid has potential anticandidal activity against clinical isolates via its antioxidant activity which turns to be modulatory effect. It has also shown synergism with the known antifungal drug FLC providing alternative combination therapy options.

17.2.7 Hydroxybenzoic Acids

This class represents the phenolic metabolites of general structure C6 $\pm$ C. It is naturally found in *Cocos nucifera,* vanilla, wine, *Macrotyloma uniflorum* (horse gram), and *Phyllanthus acidus* (Dey et al. 2005, Tian et al. 2009). They are found in intact tissues primarily as conjugates which after hydrolysis give rise to hydroxybenzoic acids. It has very well-known antioxidant activity and low toxicity benefits used in cosmetics industry. They are considered to be effective scavengers of free radicals and are also widely used as antimicrobial food additives and are used in modern nutrition therapies (Hubková et al. 2014). They have been also tested for the antifungal activity against *Candida* species; the results have shown synergism of

hydroxybenzoic acid with itraconazole (ITR) and hence can be used for improving the activity of known antifungal drugs (Faria et al. 2011). The most commonly studied hydroxybenzoic acids are as follows.

17.2.8 Gallic Acid

It is a 3,4,5-trihydroxybenzoic acid or trihydroxybenzoic acid commonly found in the oak barks, hazel nut, gallnuts, etc. They are found in free form or as tannins which can be hydrolyzed to gallic acid or gallotannins. They can form esters such as digallic and trigallic acids. It is formed from the 3-dehydroshikimate by the enzyme called as shikimate dehydrogenase which can produce 3,5-didehydroshikimate. It has known antimicrobial and anti-inflammatory activities which are being utilized in the pharmacological and cosmetics industries. The in vitro and in vivo activity of gallic acid was investigated by Li et al. (2017a, b). They have checked the antifungal activity on various fungal strains by using *Punica granatum* L. The results have shown the effect of gallic acid on the fungal cell membrane by targeting the sterol biosynthetic pathway which in turn affects the viability of *C. albicans*. The enzymatic activity of sterol 14a-demethylase P450 (CYP51), key enzyme in ergosterol biosynthesis, was reduced. Gallic acid which was extracted from *Buchenavia tomentosa* has been studied for its anticandidal activity on *C. albicans* and non-*albicans* species by Teodoro et al. (2015a, b). It has been also explored more for its mechanistic insights in *Candida* species. The extracts from *Vernonia cinerea* (L.) containing gallic acid have shown the antioxidant property against *C. albicans*. They have shown promising effect on virulence factor of *Candida* like biofilm and morphological transition (Brighenti et al. 2017). Gallic acid from acetone extract from *Buchenavia tomentosa* has shown the effect on cell adherence of *C. albicans* from oral epithelial cells and hyphal growth and disrupted biofilm (Teodoro et al. 2018). The solubility of gallic acid has been improved by using the cyclodextrins which results into the formation of HPβCD soluble inclusion complexes. The efficiency was enhanced to a great level which encourages the development of antifungal drugs (Teodoro et al. 2017). A nanoencapsulation approach has been used for the formation of chitosan-based edible films carrying the gallic acid nanoparticles for the direct delivery of gallic acid into matrix which can maintain its solubility and mechanical properties (Lamarra et al. 2017). A recent study on the extract from *Spondias tuberosa* fruit plant which is native to Brazil has shown anti-*Candida* activity probably by causing the hyperpolarization of mitochondrial and lysosomal membrane. Thus, this compound can be exploited more for its pharmacological applications (da Costa et al. 2018).

17.2.9 Vanillic Acid

It is a 4-hydroxy-3-methoxybenzoic acid which is oxidized form of vanillin, commonly used as flavoring agent. It is found in Chinese herb *Angelica sinensis* and is a

natural phenol in argan oil. It is formed from ferulic acid (Lesage-Meessen et al. 1996). It has antimicrobial properties. It is used as preservatives in foods due to its antimicrobial properties (Fitzgerald et al. 2004). It has also shown antifungal properties which have been tested against yeasts and filamentous fungi (Alnuaimi et al. 2013). It has been reported to have shown anticandidal activity. The mechanisms have been studied which included loss of membrane integrity and inhibition of ergosterol biosynthesis of *C. albicans*. It has also reduced the cell adhesion by 30–40% along with the biofilm formation in a concentration-dependent manner. The morphogenetic switching from yeast to hyphae was also hampered (Raut et al. 2013). Another study on candidal biofilms has shown the inhibition of biofilm formation, and the reduction was 75–80%. It showed promising effect on oral candidiasis and can be used as a potential antifungal drug.

17.2.10 Salicylic Acid

It is a lipophilic hydroxybenzoic acid which is formed during salicin metabolism. It naturally occurs in nuts, fruits, vegetables, herbs, teas, etc. It is widely used as an important component in aspirin drug which is used as an anti-inflammatory analgesic and antipyretic and to treat pain. It is used in cosmetic industries as an anti-acne and in skincare products. It is also used as antiseptic due to its antimicrobial activity. The coating of salicylic acid prevents the adherence of candidal cells with the Silastic catheters (Farber and Wolff 1993). It was also checked to be synergistic with known antifungal drug like FLC. This suggests its use in the combination therapy against *Candida* strains (Yücesoy et al. 2000). Another drug nystatin also became more potent when worked synergistically with the salicylic acid against clinical isolates of *C. albicans* (Ibezimako et al. 2003). The derived acetylsalicylic acid has significant role in reducing the biofilm as well as planktonic growth on the abiotic surfaces like polystyrene and acrylic surfaces (Alem and Douglas 2004). A similar study was also performed which shows the inhibition of formation of candidal biofilms which needs further investigation for its use in alternative therapy (Stepanović et al. 2004). The morphogenetic ability which is switching from yeast to hyphal form was also suppressed by inhibiting the formation of 3(R)-hydroxyoxylipins which are a fatty acid (Deva et al. 2001). Another virulence factor called as phospholipases which is involved in invading the host tissue by candidal cells was also found to be reduced in a study by Trofa et al. (2009). A chemosensitizing approach can be used to enhance the antifungal potential of known antifungal drugs when used synergistically with the salicylic acid and other phenolic compounds (Faria et al. 2011). But further investigations and studies are required to look more into its mechanism of action.

17.2.11 Protocatechuic Acid

It is a 3,4-dihydroxybenzoic acid which is one of the major metabolite of polyphenols in green tea. It has potential anticancer, antioxidant, antiulcer, anti-

inflammatory, antimicrobial, antidiabetic, and analgesic activities. It is extracted from barks of *Boswellia dalzielii* and leaves of *Diospyros melanoxylon.* Acai oil derived from palm tree is found to be rich in protocatechuic acid. It is also found in mushrooms and flowers which are used as beverages and in bran and grain brown rice (Kakkar and Bais 2014). It is produced during shikimate pathway and can be derived by vanillic acid and phthalic acid. It has antimicrobial activity which was tested by using the extracts from *Cirsium canum* against the *Streptococcus aureus* and *Streptococcus pneumoniae* (Kozyra et al. 2015). The extracts from barks of *Ficus ovata* containing protocatechuic acid were found to inhibit the planktonic growth of candidal cells (Kuete et al. 2009). They have been studied to possess anticandidal activity which was reviewed by Teodoro et al. (2015a, b). Further studies are required to exploit its potential to be used as potent antifungal drug.

17.2.12 Flavonoids

It is the largest family of phenolic compounds containing nearly more than 5000 hydroxylated polyphenolic compounds which have diverse important functions in plants. They are known to be involved in regulating environmental stresses, combating microbial infection, floral pigmentation, regulation of cell growth, and pollination (Kumar and Pandey 2013). They are mostly derived from fruits, vegetables, chocolate, and beverages like wine and tea. They have been shown to exhibit antidiabetic, anti-inflammatory, anticancer, antithrombogenic, antioxidant, and neuroprotective activities. They are also known to act as inhibitors for enzymes like phosphoinositide 3-kinase, xanthine oxidase (XO), cyclooxygenase (COX), and lipoxygenase. Flavonoids are considered as crucial component in a number of pharmaceutical, nutraceutical, medicinal, and cosmetic applications. The most widespread subclasses of flavonoids are flavan-3-ols (catechin), flavonols, flavanones, flavones, isoflavones, chalcones, and anthocyanins (Panche et al. 2016).

17.2.13 Epigallocatechin

It is a type of flavan-3-ol (catechin) which is highly present in green tea extract. They are also present in traces amount in fruits, nuts, etc. It has benefits for treating cancer, cardiovascular diseases, inflammatory disorders, and other ailments. It has known antibacterial, antiviral, antifungal, antitoxin, and antitumor effects too (Matsumoto et al. 2012). It is further studied for the anticandidal activity along with the other tea extracts (Chen et al. 2015).They were also known to induce apoptosis in FLC-resistant candidal strains and can also work synergistically with FLC (da Silva et al. 2014). It has been reported to inhibit the planktonic growth and can also work synergistically with the known antifungal drugs like miconazole, FLC, or amphotericin B which opens up opportunities for combination therapy for treating oral candidiasis (Ning et al. 2015). The derivative of epigallocatechin with the gallic acid, epigallocatechin gallate (EGCG), has been reported to be used as adjuvant for

antifungal therapy in candidiasis. Planktonic growth of candidal cells was reduced by 75% when treated with EGCG. Interestingly, the reduction in established candidal biofilm was found to be 80%. There was also an impairment of proteasome activity which helps in degrading the host proteins by candidal cells (Evensen and Braun 2009).

17.2.14 Kaempferol

It is a 3,4′,5,7-tetrahydroxyflavone which belongs to the subclass flavonols. It occurs in fruits, vegetables, lettuce, berries, etc. It is synthesized during phenylpropanoid pathway. It has anticancer, antidiabetic, antimicrobial, and antioxidant properties (Chen and Chen 2013). The phenolic compounds extracted from *Baseonema acuminatum* leaves containing kaempferol 3-O-(6″-galloyl)-beta-D-glucopyranoside have shown anticandidal activity (De Leo et al. 2004). The ethanolic extracts from *Bryophyllum pinnatum* containing kaempferol and its rhamnoside derivatives have been tested for its antimicrobial and antioxidant properties (Tatsimo et al. 2012). A study by Yordanov M (2008) has demonstrated the inhibition of *C. albicans* extracellular enzyme activity which is crucial for the host cell penetration. The secreted aspartyl proteinase activity and rate of cell wall protein glycosylation were effectively suppressed. The extracts from the plant *Equisetum giganteum* L. which is native to America containing kaempferol and its derivatives have shown to inhibit the adherence of candidal cells to the acrylic surfaces. These findings have good implication on the inhibition of candidal biofilms in oral candidiasis and denature stomatitis (Alavarce et al. 2015). Overexpression of efflux pump is one of the major contributor for development of multidrug resistance (MDR) in *C. albicans* (Prasad and Kapoor 2005). Two exclusively studied drug transporters in *C. albicans* are ATP-binding cassette (ABC) family and major facilitator superfamily (MFS) drug transporters. The effect of kaempferol on candidal cells was further investigated on the efflux pump activity (Shao et al. 2016). It induced the suppression of kaempferol-treated FLC-resistant candidal cells. The expression of MDR1 was effectively suppressed and also showed synergism with the FLC. Hence, this could be used as an effective drug targeting the efflux pump.

17.3 Baicalein

It is a 5,6,7-trihydroxyflavone which is extracted from *Scutellaria baicalensis* and *Oroxylum indicum* plants. It can be also found in fruits, green tea, dark chocolate, and vegetables and traditionally used in Chinese herbal medicine for chronic hepatitis. It has known antifungal, anti-inflammatory, antioxidant, anti-allergic, and anti-tumorigenic actions (Donald et al. 2012). It inhibits the lipoxygenases and possess anti-inflammatory property. It was very well studied for its anticancer property by acting on the angiogenesis, metastasis, and inflammation of cancer cells (Gao et al. 2016a, b). It has known antimicrobial activity and is known to inhibit the biofilm

formation and quorum-sensing signaling mechanism in *Staphylococcus aureus* (Chen et al. 2016). Baicalein inhibits the candidal growth by reducing the cell surface hydrophobicity (CSH) which is an important factor for the interaction between surface and candidal cells. It also inhibits the candidal biofilm by 70% at varying concentrations (Cao et al. 2008). Baicalein was also reported to induce programmed cell death via targeting the mitochondrial membrane potential (Dai et al. 2013). It was known to work synergistically with known antifungal drug amphotericin B which accelerates the apoptosis in *C. albicans* through the CaMCA1-mediated caspase pathway (Fu et al. 2011). Candidal growth and cell viability were inhibited by this compound which also shows synergism with FLC, but further studies are required to decipher the exact mechanism of its synergism (Serpa et al. 2012). A study was conducted on the in vitro activity of Plantago major extract in which baicalein is one of the major component and was found to be effectively reducing the candidal growth in a dose-dependent manner by various mechanisms. This includes the inhibition of biofilm formation, morphogenetic switching via inhibiting the hyphal development from yeast forms, and cell surface hydrophobicity (CSH) which is the major regulator of biofilm formation (Shirley et al. 2017).

17.4 Quercetin

It is a 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one which occurs in fruits, vegetables, leaves, and grains. It is the most abundant among flavonoids in nature. It is synthesized through phenylpropanoid pathway by phenylalanine as its precursor. It has beneficial effect on cardiovascular disease, cancers, chronic inflammatory disorders, asthma, high blood pressure, and viral infections (Kelly 2011). It has known antimicrobial activity against *Staphylococcus aureus* and *Clostridium botulinum*. It has been also found to be synergistic with the amphotericin B antifungal drug against the invasive fungus *Cryptococcus* (Oliveira et al. 2016). Quercetin extracted from edible lichen (*Usnea longissima*) has been investigated for its anticandidal activity. The results have shown that it induces FLC-mediated programmed apoptotic cell death of *Candida* cells by modulation of quorum-sensing molecule farnesol which is involved in hyphal development and biofilm formation. It also inhibits the virulence factors like phospholipase, proteinase, and esterase activity (Singh et al. 2015). The QS-mediated combined sensitizer (QC)-anticandidal agent is an effective strategy to combat candidal infections. Another study by Gao et al. (2016a, b) also demonstrated that quercetin assists FLC for inhibition of the biofilm formation in FLC-resistant candidal cells which is helpful in clinical management of the vulvovagibal candidiasis conditions. The pretreatment with the quercetin induces an anti-inflammatory effect via inhibiting the cytokine TNF-alpha production against *C. albicans* infection in macrophages (Cui et al. 2013).

17.5 Chalcones

They are open-chain flavonoids having (2E)-1,3-diphenylprop-2-en-1-one structure and occur in fruits, vegetables, and medicinal plants. They are basically characterized by the absence of "ring C" in the basic flavonoid skeleton structure. They are precursors in other flavonoid synthesis. They have antifungal, antibacterial, anti-inflammatory, and antitumor properties. They have important implications in nutraceutical industries due to nutritional and biological benefits. The hydroxylated chalcones have potential anticandidal activity (Batovska et al. 2007). A type of chalcone named 4-hydroxycordoin is found to inhibit the yeast to hyphae transition and biofilm formation of candidal cells. Thus, it can be helpful in preventing the candida from oral cavity and inhibit soft tissue invasion (Messier et al. 2011). Another chalcone called as 2′-hydroxy-4′-methoxychalcone worked synergistically with the FLC against the FLC-resistant candidal strains (Wang et al. 2016). The pharmacochemical work has been performed on the benzimidazolyl-chalcones for their antifungal activity against a clinical strain of pharmaco-chemoresistant *Candida albicans* strain and showed promising anticandidal activity (Songuigama et al. 2018). Cyclized chalcones and its derivatives are found to be effective and have synergistic activity with FLC against clinical isolates (Ahmad et al. 2017). A very recent study by Nim et al. (2018) has shown the chalcones as the potential compounds for improving the azole activity. The synthesis of chalcones with the azoles through condensation reactions triggers sensitizing of yeast strains overexpressing CaMdr1p and CaCdr1p transporters.

17.6 Lignans

They are polyphenols or diphenolic compounds which are found in flaxseeds, sesame seeds, legumes, whole grains, fruit, and vegetables. The secoisolariciresinol and matairesinol are the first precursors which have been identified in human diet. Lignans are the main source of dietary phytoestrogens. The secoisolariciresinol breaks down into enterolignans and enterolactone by human gut bacteria which are metabolites of food lignans (Peterson et al. 2010). They are strong antioxidants in nature and helpful in supporting the human health. They also act as free radical scavengers which reduce the cancer development. It is also involved in antiestrogenic effects which resists in binding of radicals to estrogen receptors and exerting the negative effects (Adlercreutz 2007). They have anti-inflammatory activity and can be categorized into eight subgroups as furofuran, furan, dibenzylbutane, dibenzylbutyrolactone, aryltetralin, arylnaphthalene, dibenzocyclooctadiene, and dibenzylbutyrolactol on the basis of cyclization pattern. They are also known for their antimicrobial properties against *C. albicans* and gram-positive bacteria. It has been reported that extract containing lignans from *Lindera erythrocarpa* has shown specific antifungal activity by inhibiting the chitin synthase 2 in *C. albicans* (Hwang et al. 2007). The lignan glycoside derived from *Styrax japonicus* plant has been demonstrated for its anticandidal mechanism via targeting

candidal membranes (Park et al. 2010). Some of the extensively studied lignan compounds are as follows.

17.7 Magnolol

It is a 4-allyl-2-(5-allyl-2-hydroxy-phenyl) phenol active lignan found in the bark of *Magnolia officinalis*. It has been traditionally used in Chinese and Japanese herbal medicine. It has anti-osteoporosis activity and anti-periodontal disease activity. It has pharmacological functions and has known analgesic, antianxiety, anti-tumorigenic properties (Lee et al. 2011). It has been known for its antifungal properties (Bang et al. 2000). It is one of the most exclusively studied compounds of lignans class. Previous studies have shown inhibitory effect on *Helicobacter pylori*, *Porphyromonas gingivalis*, etc. (Chang et al. 1998). It showed inhibitory effect on planktonic growth of *C. albicans* as well as on non-*albicans* species of *Candida*. It also reduces the biofilm formation by decreasing the metabolic activity in a concentration-dependent manner (Zhou et al. 2017). It also affects the cell adhesion and yeast to hyphae transition which is a key virulence factor in *C. albicans* via Ras1-cAMP-Efg1 pathway (Sun et al. 2015a, b). It was also synergistic with azoles by inducing a higher intracellular content of antifungals. It also targets candidal cells by various mechanisms such as functioning as a Cdr1p substrate and by targeting ergosterol biosynthesis (Sun et al. 2015a, b). Magnolol was also tested against clinical isolates from patients suffering from oral candidiasis. The results demonstrated ruptures depicting the disruption of cell membrane. It also causes decrease in biofilm formation by 69.5% and release of the intracellular content, which results in the swelling of the cell wall. It is nontoxic in nature and has negligible hemolytic activity which is approx. 11.9%. The docking results have also shown magnolol interacts with ergosterol in the fungal cell membranes. All these results have indicated that magnolol is a promising antifungal agent which can be considered for using in oral candidiasis (Behbehani et al. 2017).

17.8 Honokiol

It is a 2-(4-hydroxy-3-prop-2-enyl-phenyl)- 4-prop-2-enyl-phenol which can be isolated from bark and leaves of *Magnolia grandiflora* plant. It belongs to neolignan class, and due to its small size, it can interact with cell membrane proteins through intermolecular interactions (Woodbury et al. 2013). It is a structural isomer of magnolol. It has been traditionally used as a part of Eastern traditional membrane because of its high potent nature and also for its ability to also cross the blood barrier which is helpful for using in therapies. It has known anti-inflammatory, anti-tumorigenic, antithrombotic, antiviral, and antioxidant properties. The antifungal effect of honokiol was reported in a study by (Bang et al. 2000). The synergistic activity was demonstrated with the FLC, and it was found to be effective against the FLC-resistant clinical isolates of *Candida* (Jin et al. 2010), which can be beneficial

for combination therapy. Honokiol has effect on virulence factors, namely, cell adhesion, transition from yeast to hyphae, and biofilm formation through Ras1-cAMP-Efg1 pathway. It also prolonged the survival of *Candida*-infected nematodes which shows the nontoxic nature of this drug (Sun et al. 2015a, b). It also induces ROS accumulation which in turn leads to apoptosis or necrosis in candidal cells via mitochondrial dysfunction, and this will contribute to its fungicidal action (Sun et al. 2017). In a study by Sun et al. (2017), they worked on the insights into the mechanisms of its action. It has been demonstrated that honokiol induces the oxidative stress in *C. albicans*. It targets the mitochondria by mitochondrial respiratory chain C1 and induces ROS accumulation, disruption of intracellular iron homeostasis, and activation of autophagy and apoptosis signaling pathway. It can be used as a chemosensitizer and could be a cell wall perturbing agents. A recent study on the role of Hsp90-calcineurin pathway on the antifungal activity showed that Hsp90 enhances the antifungal activity of honokiol (Liao and sun 2018). Honokiol-loaded micelles were prepared by using emulsion-solvent evaporation procedure by conjugating with oligochitosan-pluronic conjugate (CS-F127) carrier. They have tested for the delivery of honokiol into the mice cells. The results have shown the increase in retention time of honokiol with low clearance rate and apparent distribution volume which enhances its pharmacokinetics property (Song et al. 2018).

17.9 Lariciresinol

It is a 4-[(2S,3R,4R)-4-[(4-hydroxy-3-methoxyphenyl)methyl]-3-(hydroxymethyl) oxolan-2-yl]-2-methoxyphenol or phenylpropanoid and found in sesame seeds and vegetables. It has known anti-inflammatory and antioxidant properties. The phenolic extract from Tylosema *esculentum* plant contains this compound that has been tested for its antimicrobial activity (Chingwaru et al. 2011). In another study, it was also tested for its antimicrobial property against the foodborne pathogen; it exerts its effect by inducing cell membrane permeabilization (Bajpai et al. 2017). The essential oil from clove containing lariciresinol has shown antifungal activity by targeting the fungal cell membrane (Pinto et al. 2009). Lariciresinol is known to be a precursor of enterolignan which is isolated from plant *Sambucus williamsii*, having medicinal property. It has anticandidal activity and thus reduces its growth and acts by disrupting the cell membrane. Its action results into depolarization of fungal membrane and lipids (Hwang et al. 2011).

17.10 Medioresinol

It is a 4-[(3S,3aR,6aR)-3-(4-hydroxy-3-methoxyphenyl)-1,3,3a,4,6,6a-hexahydrofuro [3,4-c]furan-6-yl]-2,6-dimethoxyphenol or called as a furofuran-type lignan which has been extracted from the bark of *Sambucus williamsii*. It has been used as a medicinal plant in traditional medicine due to its therapeutic properties. It has known

leishmanicidal activity and also reduces the cardiovascular disease risk. It is also known for its anti-inflammatory, antivirus, and analgesic properties and also used in the treatment of edema. The antibacterial effect was evaluated on the antibiotic-resistant species, and it was found to be synergistic with the known antibiotics such as ampicillin, cefotaxime, and chloramphenicol along with the antibiofilm activity (Hwang et al. 2013). Medioresinol has a significant antifungal activity against candidal cells. In order to evaluate its antifungal effect, the metabolic, morphological, and molecular assays have been worked to find its mode of action in *C. albicans*. Its action results in cell cycle arrest and also causes apoptosis which results in cell death. Its antioxidant activity induces ROS generation, and its accumulation leads to decreased depolarization of mitochondrial membrane. This series of action results into cytochrome c release, metacaspase activation, and phosphatidylserine externalization. It also causes morphological changes in nucleic acid and cell, resulting into nuclear fragmentation and its condensation. Overall, it induces apoptosis through a mitochondria-mediated apoptosis pathway (Hwang et al. 2012).

17.11 Nyasol

It is a 4,4′-[(1Z)-1,4-pentadiene-1,3-diyl]diphenol, or it is also known as cis-hinokiresinol extracted from *Anemarrhena asphodeloides*. It is known to inhibit the production of eicosanoids and nitric oxide in vitro and has anti-inflammatory effects (Lim et al. 2009). It is also known for its antipyretic, antidiabetic, and antidepressant properties. It has anti-oocyte property against the mycelial growth of *Colletotrichum orbiculare* and *Phytophthora capsici* (Park et al. 2003). Nyasol exhibits antimicrobial activity against pathogens. Its antifungal activity has been reported in a study by Iida et al. (2000). Nyasol has been extracted from *Anemarrhena asphodeloides* and has shown antifungal activity against *C. albicans*, *Aspergillus fumigatus*, and *Trichophyton mentagrophytes*. It was also found to be synergistic with known azoles like miconazole, clotrimazole, and ketoconazole, among the other azoles. This finding can contribute for its usage as adjuvant in combination therapy.

17.12 Other Classes

17.12.1 Coumarins

They are benzopyrones which contain benzene and α-pyrone rings that can be isolated from tonka bean, vanilla grass, cinnamon, etc. The naturally occurring derivatives are umbelliferone (7-hydroxycoumarin), herniarin (7-methoxycoumarin), esculetin (6,7-dihydroxycoumarin), psoralen, and imperatorin. They have been used in the treatment of lymphedema, and they have the ability to increase the antithrombin levels in plasma. It is also used for reduction

of uric acid in blood by increasing the excretion of uric acid in urine. They are also used in cosmetic, perfumery, and household products due to its biological and pharmacological properties. Warfarin is a very well-known oral anticoagulant. It also has anti-inflammatory, antiulcerogenic, antifilarial, and antibacterial properties (Kontogiorgis and Hadjipavlou-Litina 2003). Later on, its antifungal properties have been evaluated and found to be effective against *C. albicans*, *Aspergillus fumigatus*, and *Fusarium solani.* The potential coumarins and its derivatives are osthole, osthenol, xanthotoxin, oroselone, etc. (Montagner et al. 2008). Osthole is a natural coumarin which has shown strong anticandidal activity. It has also shown synergism with FLC against FLC-resistant *C. albicans* in vitro and also indicated the endogenous ROS augmentation which contributes to the synergism of FLC and osthole (Li et al. 2017a, b). Another coumarins such as robustic acid and thonningine-C which were isolated from *Millettia thonningii* have shown fungicidal activity against the *C. albicans.* The molecular modelling studies have shown the binding of these compounds to the active site in turn disrupts the sterol synthesis (Ayine-Tora et al. 2016). The phosphoramidate derivatives of coumarin have also shown promising antifungal activity by acting as chitin synthase inhibitors (Ji et al. 2016).

17.12.2 Xanthones

They are 9H-xanthen-9-ones, which are heterocyclic compounds based on the dibenzo-c-pyrone scaffold. They have pharmacological properties, including antitumor, antioxidant, anti-allergic, anti-inflammatory, and antimicrobial activities. They are categorized into simple oxygenated and prenylated polycyclic dehydroxanthones. The alpha-mangostin was known to have antifungal activity and can be considered for treating oral candidiasis due to its low toxicity (Kaomongkolgit et al. 2009). It also inhibits the biofilm formation (Kaomongkolgit and Jamdee 2017). The antifungal activity of simple oxygenated xanthones was evaluated and demonstrated to act by inhibiting the ergosterol biosynthesis (Pinto et al. 2011). The extracts from *Hypericum tetrapterum* plant containing 1,7-dihydroxyxanthone have shown strong anticandidal activity (Zubricka et al. 2015).

17.13 Conclusion

Phytophenolics have great potential to inhibit the candidal growth. Several mechanisms have been studied through which these phenolic compounds can hinder the growth of *C. albicans* or work synergistically with known antifungal drugs (Table 17.1). They are broad class of compounds which are proven to be potent in combating fungal infections. Considering the fact that synthesis of new drugs is a cumbersome process, there is a need to search more on the structural and functional mode of action of phytophenolics to exploit their phytotherapeutic potential.

Table 17.1 Summary of anticandidal phenolic compounds with their mode of actions

Name of the class	Name of the compound	Mode of action	References
Hydroxycinnamic acids	Caffeic acid	Inhibits biofilm formation	De Vita et al. (2014)
		Synergism with FLC	De Vita et al. (2014)
		Synergism with Caspofungin	Sun et al. (2018)
		Mitochondrial dysfunction	Sun et al. (2018)
		Impaired glyoxylate cycle	Cheah et al. (2014)
	p-Coumaric acid	Inhibits candidal growth	Cheah et al. (2014)
	Ferulic acid	Synergism with caspofungin	Canturk (2018)
		Induces apoptosis	Canturk (2018)
		Inhibits biofilm formation	Panwar et al. (2016)
	Sinapic acid	Inhibits oxidation	Chen (2016)
	Rosmarinic acid	Synergism with FLC	Zou et al. (2002)
		Antioxidant action	Calixto et al. (2015)
Hydroxybenzoic acids	Gallic acid	Antioxidant action	Brighenti et al. (2017)
		Inhibits biofilm formation	Brighenti et al. (2017)
		Inhibits morphogenetic switching	Teodoro et al. (2012; 2018)
		Reduces cell adherence	Brighenti et al. (2017)
		Mitochondrial dysfunction	Teodoro et al. (2012; 2018)
		Disrupts lysosomal membrane integrity	da Costa et al. (2018)
	Vanillic acid	Inhibits ergosterol biosynthesis	Raut et al. (2013)
		Disrupts cell membrane integrity	Alnuaimi et al. (2013)
		Reduces cell adherence	Raut et al. (2013)
		Inhibits morphogenetic switching	Raut et al. (2013)
		Inhibits biofilm formation	Raut et al. (2013)
	Salicylic acid	Synergism with FLC	Yücesoy et al. (2000)
		Synergism with nystatin	Alem and Douglas (2004)
		Inhibits planktonic growth	Alem and Dougles (2004)
		Inhibits biofilm formation	Alem and Dougles (2004)

(continued)

Table 17.1 (continued)

Name of the class	Name of the compound	Mode of action	References
		Inhibits morphogenetic switching	Stepanović et al. (2004)
		Reduces phospholipases activity	Deva et al. (2001) Trofa et al. (2009)
	Protocatechuic acid	Inhibits planktonic growth	Kuete et al. (2009)
Flavonoids	Epigallocatechin	Synergism with FLC Synergism with miconazole Synergism with amphotericin B Inhibits biofilm formation Reduces proteasome activity	da Silva et al. (2014) Ning et al. (2015) Ning et al. (2015) Ning et al. (2015) Evensen and Braun (2009)
	Kaempferol	Reduces aspartyl proteinase activity Reduces protein glycosylation Inhibits biofilm formation Reduces cell adherence Targets overexpression of efflux pumps	Tatsimo et al. (2012) Tatsimo et al. (2012) Alavarce et al. (2015) Alavarce et al. (2015) Shao et al. (2016)
	Baicalein	Reduces cell surface hydrophobicity Inhibits biofilm formation Mitochondrial dysfunction Induces apoptosis Synergism with amphotericin B Synergism with FLC Inhibits morphogenetic switching	Chen et al. (2016) and Shirley et al. (2017) Chen et al. (2016) and Shirley et al. (2017) Dai et al. (2013) and Fu et al. (2011) Fu et al. (2011) Fu et al. (2011) Serpa et al. (2012) Shirley et al. (2017) Shirley et al. (2017)
	Quercetin	Synergism with amphotericin B Modulation of quorum sensing Inhibits morphogenetic switching Induces apoptosis Inhibits biofilm formation Reduces phospholipase activity Reduces proteinase activity Synergism with FLC	Oliveira et al. (2016) Singh et al. (2015) Singh et al. (2015) Singh et al. (2015) Singh et al. (2015) Singh et al. (2015) Singh et al. (2015) Gao et al. (2016a, b)

(continued)

Table 17.1 (continued)

Name of the class	Name of the compound	Mode of action	References
	Chalcones	Inhibits morphogenetic switching Inhibits biofilm formation Synergism with FLC Targets efflux pumps	Messier et al. (2011) Wang et al. (2016) Songuigama et al. (2018) Nim et al. (2018)
Lignans	Magnolol	Inhibits morphogenetic switching Reduces cell adherence Inhibits biofilm formation Synergism with FLC Targets efflux pump Inhibits ergosterol biosynthesis Disrupts cell membrane integrity	Sun et al. (2015a, b) Sun et al. (2015a, b) Sun et al. (2015a, b) Behbehani et al. (2017) Sun et al. (2015a, b) Behbehani et al. (2017) Behbehani et al. (2017)
	Honokiol	Synergism with FLC Inhibits morphogenetic switching Reduces cell adherence Inhibits biofilm formation Induces apoptosis Induces oxidative stress Mitochondrial dysfunction Disrupts cell membrane	Jin et al. (2010) Sun et al. (2015a, b) Sun et al. (2015a, b) Sun et al. (2017) Sun et al. (2017) Sun et al. (2017) Sun et al. (2017) Sun et al. (2017)
	Lariciresinol	Cell membrane permeabilization Lipid depolarization	Bajpai et al. (2017) Pinto et al. (2009)
	Medioresinol	Synergism with chloramphenicol Inhibits biofilm formation Cell cycle arrest ROS generation Mitochondrial dysfunction Phosphatidylserine externalization DNA, nuclear fragmentation Induces apoptosis	Hwang et al. (2012) Hwang et al. (2012) Hwang et al. (2012) Hwang et al. (2012) Hwang et al. (2012) Hwang et al. (2012) Hwang et al. (2012)
	Nyasol	Synergism with miconazole Synergism with	Iida et al. (2000) Iida et al. (2000)

(continued)

Table 17.1 (continued)

Name of the class	Name of the compound	Mode of action	References
		clotrimazole Synergism with ketoconazole Reduces planktonic growth	Iida et al. (2000) Iida et al. (2000)
Coumarins	Osthole	Synergism with FLC ROS generation	Li et al. (2017a, b) Li et al. (2017a, b)
	Robustic acid	Inhibits sterol synthesis	Ayine-Tora et al. (2016)
	Phosphoramidate derivatives	Inhibits chitin synthesis	Ji et al. (2016)
Xanthones	Alpha-mangostin	Inhibits biofilm formation Inhibits ergosterol biosynthesis	Kaomongkolgit et al. (2009) Pinto et al. (2011)

Conflict of Interest None to declare

References

Adlercreutz H (2007) Lignans and human health. Crit Rev Clin Lab Sci 44:483–525

Ahmad A, Wani MY, Patel M, Sobral AJFN, Duse AG, Aqlan FM, Al-Bogami AS (2017) Synergistic antifungal effect of cyclized chalcone derivatives and fluconazole against *Candida albicans*. Medchemcomm 8:2195–2207

Alam MA, Subhan N, Hossain H, Hossain M, Reza HM, Rahman MM, Ullah MO (2016) Hydroxycinnamic acid derivatives: a potential class of natural compounds for the management of lipid metabolism and obesity. Nutr Metab (Lond) 11:13–27

Alavarce RA, Saldanha LL, Almeida NL, Porto VC, Dokkedal AL, Lara VS (2015) The beneficial effect of *Equisetum giganteum* L. against Candida biofilm formation: new approaches to denture stomatitis. Evid Based Complement Alternat Med 2015:939625

Alem MA, Douglas LJ (2004) Effects of aspirin and other nonsteroidal anti-inflammatory drugs on biofilms and planktonic cells of *Candida albicans*. Antimicrob Agents Chemother 48:41–47

Alnuaimi AD, O'Brien-Simpson NM, Reynolds EC, McCullough MJ (2013) Clinical isolates and laboratory reference Candida species and strains have varying abilities to form biofilms. FEMS Yeast Res 13:689–699

Ansari MA, Anurag A, Fatima Z, Hameed S (2013) Natural phenolic compound: A potential antifungal target. In: Mendez-Vilas A (ed) Microbial pathogens and strategies for combating them: science, technology and education. Formatex Research Center, Badajoz, pp 1189–1195

Ayine-Tora DM, Kingsford-Adaboh R, Asomaning WA, Harrison JJ, Mills-Robertson FC, Bukari Y, Sakyi PO, Kaminta S, Reynisson J (2016) Coumarin antifungal Lead compounds from *Millettia thonningii* and their predicted mechanism of action. Molecules 21:E1369

Bajpai VK, Shukla S, Paek WK, Lim J, Kumar P, Kumar P, Na M (2017) Efficacy of (+)-Lariciresinol to control bacterial growth of *Staphylococcus aureus* and *Escherichia coli* O157: H. Front Microbiol 8:804

Bang KH, Kim YK, Min BS, Na MK, Rhee YH, Lee JP, Bae KH (2000) Antifungal activity of magnolol and honokiol. Arch Pharm Res 23:46–49

Batovska D, Parushev S, Slavova A, Bankova V, Tsvetkova I, Ninova M, Najdenski H (2007) Study on the substituents' effects of a series of synthetic chalcones against the yeast *Candida albicans*. Eur J Med Chem 42:87–92

Behbehani J, Shreaz S, Irshad M, Karched M (2017) The natural compound magnolol affects growth, biofilm formation, and ultrastructure of oral Candida isolates. Microb Pathog 113:209–217

Brighenti FL, Salvador MJ, Gontijo AVL, Delbem ACB, Delbem ÁCB, Soares CP, de Oliveira MAC, Girondi CM, Koga-Ito CY (2017) Plant extracts: initial screening, identification of bioactive compounds and effect against *Candida albicans* biofilms. Future Microbiol 12:15–27

Calixto Júnior JT, Morais SM, Martins CG, Vieira LG, Morais-Braga MF, Carneiro JN, Machado AJ, Menezes IR, Tintino SR, Coutinho HD (2015) Phytochemical analysis and modulation of antibiotic activity by Luehea paniculata Mart. & Zucc. (Malvaceae) in multiresistant clinical isolates of Candida spp. Biomed Res Int 2015:807670

Canturk Z (2018) Evaluation of synergistic anticandidal and apoptotic effects of ferulic acid and caspofungin against *Candida albicans*. J Food Drug Anal 1:439–443

Cao Y, Dai B, Wang Y, Huang S, Xu Y, Cao Y, Gao P, Zhu Z, Jiang Y (2008) In vitro activity of baicalein against *Candida albicans* biofilms. Int J Antimicrob Agents 32:73–77

Chang B, Lee Y, Ku Y, Bae K, Chung C (1998) Antimicrobial activity of magnolol and honokiol against periodontopathic microorganisms. Planta Med 64:367–369

Cheah HL, Lim V, Sandai D (2014) Inhibitors of the glyoxylate cycle enzyme ICL1 in *Candida albicans* for potential use as antifungal agents. PLoS One 9:e95951

Chen C (2016) Sinapic acid and its derivatives as medicine in oxidative stress-induced diseases and aging. Oxidative Med Cell Longev 2016:3571614

Chen AY, Chen YC (2013) A review of the dietary flavonoid, kaempferol on human health and cancer chemoprevention. Food Chem 138:2099–2107

Chen M, Zhai L, Arendrup MC (2015) In vitro activity of 23 tea extractions and epigallocatechin gallate against Candida species. Med Mycol 53:194–198

Chen Y, Liu T, Wang K, Hou C, Cai S, Huang Y, Du Z, Huang H, Kong J, Chen Y (2016) Baicalein inhibits *Staphylococcus aureus* biofilm formation and the quorum sensing system in vitro. PLoS One 11:e0153468

Chingwaru W, Duodu G, Zyl YV, Schoeman CJ, Majinda RT, Yeboah SO, Jackson J, Kapewangolo PT, Kandawa-Schulz M, Minnaar A, Cencic A (2011) Antibacterial and anticandidal activity of *Tylosema esculentum* (marama) extracts. S Afr J Sci 107:1–11

Cui S, Qian J, Bo P (2013) Inhibitive effect on phagocytosis of *Candida albicans* induced by pretreatment with quercetin via actin cytoskeleton interference. J Tradit Chin Med 33:804–809

da Costa Cordeiro BMP, de Lima Santos ND, Ferreira MRA, de Araújo LCC, Junior ARC, da Conceição Santos AD, de Oliveira AP, da Silva AG, da Silva Falcão EP, Dos Santos Correia MT, da Silva Almeida JRG, da Silva LCN, Soares LAL, Napoleão TH, da Silva MV, Paiva PMG (2018) Hexane extract from Spondias tuberosa (Anacardiaceae) leaves has antioxidant activity and is an anti-Candida agent by causing mitochondrial and lysosomal damages. BMC Complement Altern Med 18:284

da Silva CR, de Andrade Neto JB, de Sousa CR, Figueiredo NS, Sampaio LS, Magalhães HI, Cavalcanti BC, Gaspar DM, de Andrade GM, Lima IS, de Barros Viana GS, de Moraes MO, Lobo MD, Grangeiro TB, Nobre Júnior HV (2014) Synergistic effect of the flavonoid catechin, quercetin, or epigallocatechin gallate with fluconazole induces apoptosis in *Candida tropicalis* resistant to fluconazole. Antimicrob Agents Chemother 58:1468–1478

Dai BD, Wang Y, Zhao LX, Li DD, Li MB, Cao YB, Jiang YY (2013) Cap1p attenuates the apoptosis of *Candida albicans*. FEBS J 280:2633–2643

De Leo M, Braca A, De Tommasi N, Norscia I, Morelli I, Battinelli L, Mazzanti G (2004) Phenolic compounds from *Baseonema acuminatum* leaves: isolation and antimicrobial activity. Planta Med 70:841–846

De Vita D, Friggeri L, D'Auria FD, Pandolfi F, Piccoli F, Panella S, Palamara AT, Simonetti G, Scipione L, Di Santo R, Costi R, Tortorella S (2014) Activity of caffeic acid derivatives against *Candida albicans* biofilm. Bioorg Med Chem Lett 24:1502–1505

Deva R, Ciccoli R, Kock L, Nigam S (2001) Involvement of aspirin-sensitive oxylipins in vulvovaginal candidiasis. FEMS Microbiol Lett 198:37–43

Dey G, Chakraborty M, Mitra A (2005) Profiling C6-C3 and C6-C1 phenolic metabolites in *Cocos nucifera*. J Plant Physiol 162:375–381

Donald G, Hertzer K, Eibl G (2012) Baicalein--an intriguing therapeutic phytochemical in pancreatic cancer. Curr Drug Targets 13:1772–1776

El-Seedi HR, El-Said AM, Khalifa SA, Göransson U, Bohlin L, Borg-Karlson AK, Verpoorte R (2012) Biosynthesis, natural sources, dietary intake, pharmacokinetic properties, and biological activities of hydroxycinnamic acids. J Agric Food Chem 60:10877–10895

Evensen NA, Braun PC (2009) The effects of tea polyphenols on *Candida albicans*: inhibition of biofilm formation and proteasome inactivation. Can J Microbiol 55:1033–1039

Farber BF, Wolff AG (1993) Salicylic acid prevents the adherence of bacteria and yeast to silastic catheters. J Biomed Mater Res 27:599–602

Faria NC, Kim JH, Gonçalves LA, Martins Mde L, Chan KL, Campbell BC (2011) Enhanced activity of antifungal drugs using natural phenolics against yeast strains of Candida and Cryptococcus. Lett Appl Microbiol 52:506–513

Fitzgerald DJ, Stratford M, Gasson MJ, Ueckert J, Bos A, Narbad A (2004) Mode of antimicrobial action of vanillin against *Escherichia coli, Lactobacillus plantarum* and *Listeria innocua*. J Appl Microbiol 97:104–113

Fu Z, Lu H, Zhu Z, Yan L, Jiang Y, Cao Y (2011) Combination of baicalein and Amphotericin B accelerates *Candida albicans* apoptosis. Biol Pharm Bull 34:214–218

Gao Y, Snyder SA, Smith JN, Chen YC (2016a) Anticancer properties of baicalein: a review. Med Chem Res 25:1515–1523

Gao M, Wang H, Zhu L (2016b) Quercetin assists fluconazole to inhibit biofilm formations of fluconazole-resistant *Candida albicans* in in vitro and in vivo antifungal managements of Vulvovaginal candidiasis. Cell Physiol Biochem 40:727–742

Hubková B, Veliká B, Birková A, Guzy J, Mareková M (2014) Hydroxybenzoic acids and their derivatives as peroxynitrite scavengers. Free Radic Biol Med 75:S33–S34

Hwang EI, Lee YM, Lee SM, Yeo WH, Moon JS, Kang TH, Park KD, Kim SU (2007) Inhibition of chitin synthase 2 and antifungal activity of lignans from the stem bark of Lindera erythrocarpa. Planta Med 73:679–682

Hwang B, Cho J, Hwang IS, Jin HG, Woo ER, Lee DG (2011) Antifungal activity of lariciresinol derived from *Sambucus williamsii* and their membrane-active mechanisms in *Candida albicans*. Biochem Biophys Res Commun 410:489–493

Hwang JH, Hwang IS, Liu QH, Woo ER, Lee DG (2012) (+)-Medioresinol leads to intracellular ROS accumulation and mitochondria-mediated apoptotic cell death in *Candida albicans*. Biochimie 94:1784–1793

Hwang JH, Choi H, Hwang IS, Kim AR, Woo ER, Lee DG (2013) Synergistic antibacterial and antibiofilm effect between (+)-medioresinol and antibiotics in vitro. Appl Biochem Biotechnol 170:1934–1941

Ibezimako EC, Esimone CO, Ofokansi KC, Oragui CI (2003) Evaluation of the antifungal properties of nystatin-salicylic acid combinations against clinical isolates of *Candida albicans*. J Biomed Invest 2003:10–17

Iida Y, Oh KB, Saito M, Matsuoka H, Kurata H (2000) In vitro synergism between nyasol, an active compound isolated from *Anemarrhena asphodeloides*, and azole agents against *Candida albicans*. Planta Med 66:435–438

Ji Q, Ge Z, Ge Z, Chen K, Wu H, Liu X, Huang Y, Yuan L, Yang X, Liao F (2016) Synthesis and biological evaluation of novel phosphoramidate derivatives of coumarin as chitin synthase inhibitors and antifungal agents. Eur J Med Chem 108:166–176

Jin J, Guo N, Zhang J, Ding Y, Tang X, Liang J, Li L, Deng X, Yu L (2010) The synergy of honokiol and fluconazole against clinical isolates of azole-resistant *Candida albicans*. Lett Appl Microbiol 51:351–357

Kakkar S, Bais S (2014) A review on protocatechuic acid and its pharmacological potential. ISRN Pharmacol 2014:952943

Kaomongkolgit R, Jamdee K (2017) Inhibitory effect of alpha-mangostin on Candida biofilms. Odontology 105:248–253

Kaomongkolgit R, Jamdee K, Chaisomboon N (2009) Antifungal activity of alpha-mangostin against *Candida albicans*. J Oral Sci 51:401–406

Kelly GS (2011) Quercetin. Monograph Altern Med Rev 16:172–194

Kelly C, Jones O, Barnhart C, Lajoie C (2008) Effect of furfural, vanillin and syringaldehyde on *Candida guilliermondii* growth and xylitol biosynthesis. Appl Biochem Biotechnol 148:97–108

Kim J, Sudbery P (2011) *Candida albicans*, a major human fungal pathogen. J Microbiol 49:171–177

Kontogiorgis C, Hadjipavlou-Litina D (2003) Biological evaluation of several coumarin derivatives designed as possible anti-inflammatory/antioxidant agents. J Enzyme Inhib Med Chem 18:63–69

Kozyra M, Biernasiuk A, Malm A, Chowaniec M (2015) Chemical compositions and antibacterial activity of extracts obtained from the inflorescences of Cirsium canum (L.) all. Nat Prod Res 29:2059–2063

Ksouri R, Ksouri WM, Jallali I, Debez A, Magné C, Hiroko I, Abdelly C (2012) Medicinal halophytes: potent source of health promoting biomolecules with medical, nutraceutical and food applications. Crit Rev Biotechnol 32:289–326

Kuete V, Nana F, Ngameni B, Mbaveng AT, Keumedjio F, Ngadjui BT (2009) Antimicrobial activity of the crude extract, fractions and compounds from stem bark of Ficus ovata (Moraceae). J Ethnopharmacol 124:556–561

Kumar S, Pandey AK (2013) Chemistry and biological activities of flavonoids: an overview. Sci World J 2013:162750

Kuwahara H, Kanazawa A, Wakamatu D, Morimura S, Kida K, Akaike T, Maeda H (2004) Antioxidative and antimutagenic activities of 4-vinyl-2,6-dimethoxyphenol (canolol) isolated from canola oil. J Agric Food Chem 52:4380–4387

Lamarra J, Giannuzzi L, Rivero S, Pinotti A (2017) Assembly of chitosan support matrix with gallic acid-functionalized nanoparticles. Mater Sci Eng C Mater Biol Appl 79:848–859

Lee YJ, Lee YM, Lee CK, Jung JK, Han SB, Hong JT (2011) Therapeutic applications of compounds in the Magnolia family. Pharmacol Ther 130:157–176

Lesage-Meessen L, Delattre M, Haon M, Thibault JF, Ceccaldi BC, Brunerie P, Asther M (1996) A two-step bioconversion process for vanillin production from ferulic acid combining *Aspergillus niger* and *Pycnoporus cinnabarinus*. J Biotechnol 50:107–113

Li ZJ, Liu M, Dawuti G, Dou Q, Ma Y, Liu HG, Aibai S (2017a) Antifungal activity of Gallic acid in vitro and in vivo. Phytother Res 31:1039–1045

Li DD, Chai D, Huang XW, Guan SX, Du J, Zhang HY, Sun Y, Jiang YY (2017b) Potent in vitro synergism of fluconazole and Osthole against fluconazole-resistant *Candida albicans*. Antimicrob Agents Chemother 61:e00436–e00417

Liao K, Sun L (2018) Roles of the Hsp90-Calcineurin pathway in the antifungal activity of Honokiol. J Microbiol Biotechnol 28:1086–1093

Lim H, Nam JW, Seo EK, Kim YS, Kim HP (2009) (−)-Nyasol (cis-hinokiresinol), a norneolignan from the rhizomes of *Anemarrhena asphodeloides*, is a broad spectrum inhibitor of eicosanoid and nitric oxide production. Arch Pharm Res 32:1509–1514

Matsumoto Y, Kaihatsu K, Nishino K, Ogawa M, Kato N, Yamaguchi A (2012) Antibacterial and antifungal activities of new acylated derivatives of epigallocatechin gallate. Front Microbiol 3:53

Messier C, Epifano F, Genovese S, Grenier D (2011) Inhibition of *Candida albicans* biofilm formation and yeast-hyphal transition by 4-hydroxycordoin. Phytomedicine 18:380–383

Montagner C, de Souza SM, Groposoa C, Delle Monache F, Smânia EF, Smânia A Jr (2008) Antifungal activity of coumarins. Z Naturforsch C 63:21–28

Nim S, Baghel P, Tran-Nguyen VK, Peres B, Nguyen KA, Pietro AD, Falson P, Prasad R, Boumendjel A (2018) Make azoles active again: chalcones as potent reversal agents of transporters-mediated resistance in *Candida albicans*. Future Med Chem 10:2177–2186

Ning Y, Ling J, Wu CD (2015) Synergistic effects of tea catechin epigallocatechin gallate and antimycotics against oral Candida. Arch Oral Biol 60:1565–1570

Oliveira VM, Carraro E, Auler ME, Khalil NM (2016) Quercetin and rutin as potential agents antifungal against Cryptococcus spp. Braz J Biol 76:1029–1034

Panche AN, Diwan AD, Chandra SR (2016) Flavonoids: an overview. J Nutr Sci 5:e47

Panwar R, Pemmaraju SC, Sharma AK, Pruthi V (2016) Efficacy of ferulic acid encapsulated chitosan nanoparticles against *Candida albicans* biofilm. Microb Pathog 95:21–31

Park HJ, Lee JY, Moon SS, Hwang BK (2003) Isolation and anti-oomycete activity of nyasol from Anemarrhena asphodeloides rhizomes. Phytochemistry 64:997–1001

Park C, Woo ER, Lee DG (2010) Anti-Candida property of a lignan glycoside derived from *Styrax japonica S*. et Z. via membrane-active mechanisms. Mol Cells 29:581–584

Peterson J, Dwyer J, Adlercreutz H, Scalbert A, Jacques P, McCullough ML (2010) Dietary lignans: physiology and potential for cardiovascular disease risk reduction. Nutr Rev 68:571–603

Pierce GE (2005) Pseudomonas aeruginosa, Candida albicans, and device-related nosocomial infections: implications, trends, and potential approaches for control. J Ind Microbiol Biotechnol 32:309–318

Pinto E, Vale-Silva L, Cavaleiro C, Salgueiro L (2009) Antifungal activity of the clove essential oil from *Syzygium aromaticum* on Candida, Aspergillus and dermatophyte species. J Med Microbiol 58:1454–1462

Pinto E, Afonso C, Duarte S, Vale-Silva L, Costa E, Sousa E, Pinto M (2011) Antifungal activity of xanthones: evaluation of their effect on ergosterol biosynthesis by high-performance liquid chromatography. Chem Biol Drug Des 77:212–222

Prasad R, Kapoor K (2005) Multidrug resistance in yeast Candida. Int Rev Cytol 242:215–248

Raut JS, Rajput SB, Shinde RB, Surwase BS, Karuppayil SM (2013) Vanillin inhibits growth, morphogenesis and biofilm formation by *Candida albicans*. T.B.P.A 3:130–138

Serpa R, França EJ, Furlaneto-Maia L, Andrade CG, Diniz A, Furlaneto MC (2012) In vitro antifungal activity of the flavonoid baicalein against Candida species. J Med Microbiol 61:1704–1708

Shao J, Zhang M, Wang T, Li Y, Wang C (2016) The roles of CDR1, CDR2, and MDR1 in kaempferol-induced suppression with fluconazole-resistant *Candida albicans*. Pharm Biol 54:984–992

Shirley KP, Windsor LJ, Eckert GJ, Gregory RL (2017) In vitro effects of Plantago Major extract, Aucubin, and Baicalein on *Candida albicans* biofilm formation, metabolic activity, and cell surface hydrophobicity. J Prosthodont 26:508–515

Singh BN, Upreti DK, Singh BR, Pandey G, Verma S, Roy S, Naqvi AH, Rawat AK (2015) Quercetin sensitizes fluconazole-resistant Candida albicans to induce apoptotic cell death by modulating quorum sensing. Antimicrob Agents Chemother 59:2153–2168

Song Z, Sun J, Deng P, Zhou F, Xu H, Wen Y, Teng F, Ge D, Feng R (2018) Oligochitosan-pluronic 127 conjugate for delivery of honokiol. Artif Cells Nanomed Biotechnol 5:1–11

Songuigama C, Jean-Paul ND, Mamidou KW, Drissa S, Mahama Q (2018) Anticandidosic activities of new Chalcones vectorised by Benzimidazole against strain of *Candida Albicans* Pharmacoresistance to azoles. IOSR-JPBS 13:11–16

Stalmach A (2014) Bioavailability of dietary anthocyanins and hydroxycinnamic acids trans. In: Watson RR, Preedy VR, Zibadi S (eds) . Polyphenols in Human Health and Disease Academic, San Diego, pp 561–576

Stepanović S, Vuković D, Jesić M, Ranin L (2004) Influence of acetylsalicylic acid (aspirin) on biofilm production by Candida species. J Chemother 16:134–138

Sun L, Liao K, Wang D (2015a) Effects of magnolol and honokiol on adhesion, yeast-hyphal transition, and formation of biofilm by *Candida albicans*. PLoS One 10:e0117695

Sun LM, Liao K, Liang S, Yu PH, Wang DY (2015b) Synergistic activity of magnolol with azoles and its possible antifungal mechanism against *Candida albicans*. J Appl Microbiol 118:826–838

Sun L, Liao K, Wang D (2017) Honokiol induces superoxide production by targeting mitochondrial respiratory chain complex I in *Candida albicans*. PLoS One 12:e0184003

Sun L, Liao K, Hang C (2018) Caffeic acid phenethyl ester synergistically enhances the antifungal activity of fluconazole against resistant *Candida albicans*. Phytomedicine 40:55–58

Tatsimo SJ, Tamokou Jde D, Havyarimana L, Csupor D, Forgo P, Hohmann J, Kuiate JR, Tane P (2012) Antimicrobial and antioxidant activity of kaempferol rhamnoside derivatives from *Bryophyllum pinnatum*. BMC Res Notes 5:158

Teixeira J, Gaspar A, Garrido EM, Garrido J, Borges F (2013) Hydroxycinnamic acid antioxidants: an electrochemical overview. Biomed Res Int 2013:251754

Teodoro GR, Ellepola K, Seneviratne CJ, Koga-Ito CY (2015a) Potential use of phenolic acids as anti-Candida agents: A review. Front Microbiol 6:1420

Teodoro GR, Brighenti FL, Delbem AC, Delbem ÁC, Khouri S, Gontijo AV, Pascoal AC, Salvador MJ, Koga-Ito CY (2015b) Antifungal activity of extracts and isolated compounds from *Buchenavia tomentosa* on *Candida albicans* and non-albicans. Future Microbiol 10:917–927

Teodoro GR, Gontijo AVL, Borges AC, Tanaka MH, Lima GMG, Salvador MJ, Koga-Ito CY (2017) Gallic acid/hydroxypropyl-β-cyclodextrin complex: improving solubility for application on in vitro/ in vivo *Candida albicans* biofilms. PLoS One 12:e0181199

Teodoro GR, Gontijo AVL, Salvador MJ, Tanaka MH, Brighenti FL, Delbem ACB, Delbem ÁCB, Koga-Ito CY (2018) Effects of acetone fraction from Buchenavia tomentosa aqueous extract and Gallic acid on *Candida albicans* biofilms and virulence factors. Front Microbiol 9:647

Tian RR, Pan QH, Zhan JC, Li JM, Wan SB, Zhang QH, Huang WD (2009) Comparison of phenolic acids and Flavan-3-ols during wine fermentation of grapes with different harvest times. Molecules 14:827–838

Trofa D, Agovino M, Stehr F, Schäfer W, Rykunov D, Fiser A, Hamari Z, Nosanchuk JD, Gácser A (2009) Acetylsalicylic acid (aspirin) reduces damage to reconstituted human tissues infected with Candida species by inhibiting extracellular fungal lipases. Microbes Infect 11:1131–1139

Wang YH, Dong HH, Zhao F, Wang J, Yan F, Jiang YY, Jin YS (2016) The synthesis and synergistic antifungal effects of chalcones against drug resistant *Candida albicans*. Bioorg Med Chem Lett 26:3098–3102

Woodbury A, Yu SP, Wei L, García P (2013) Neuro-modulating effects of honokiol: a review. Front Neurol 4:130

Yücesoy M, Oktem IM, Gülay Z (2000) In-vitro synergistic effect of fluconazole with nonsteroidal anti-inflammatory agents against *Candida albicans* strains. J Chemother 12:385–389

Zhou P, Fu J, Hs H, Liu X (2017) In vitro inhibitory activities of magnolol against Candida spp. Drug Des Devel Ther 11:2653–2661

Zou Y, Kim AR, Kim JE, Choi JS, Chung HY (2002) Peroxynitrite scavenging activity of sinapic acid (3,5-dimethoxy-4-hydroxycinnamic acid) isolated from *Brassica juncea*. J Agric Food Chem 50:5884–5890

Zubricka D, Mišianikova A, Henzelyova J, Valletta A, De Angelis G, D'Auria FD, Simonetti G, Pasqua G, Čellarova E (2015) Xanthones from roots, hairy roots and cell suspension cultures of selected Hypericum species and their antifungal activity against *Candida albicans*. Plant Cell Rep 34:1953–1962