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Natural products targeting the synthesis of β(1,3)-D-glucan and chitin of the fungal cell wall. Existing drugs and recent findings

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ABSTRACT

Background: During the last three decades systemic fungal infections associated to immunosuppressive therapies have become a serious healthcare problem. Clinical development of new antifungals is an urgent requirement. Since fungal but not mammalian cells are encased in a carbohydrate-containing cell wall, which is required for the growth and viability of fungi, the inhibition of cell wall synthesizing machinery, such as β(1,3)-D-glucan synthases (GS) and chitin synthases (CS) that catalyze the synthesis of β(1-3)-D-glucan and chitin, respectively, represent an ideal mode of action of antifungal agents. Although the echinocandins anidulafungin, caspofungin and micafungin are clinically well-established GS inhibitors for the treatment of invasive fungal infections, much effort must still be made to identify inhibitors of other enzymes and processes involved in the synthesis of the fungal cell wall.

Purpose: Since natural products (NPs) have been the source of several antifungals in clinical use and also have provided important scaffolds for the development of semisynthetic analogues, this review was devoted to investigate the advances made to date in the discovery of NPs from plants that showed capacity of inhibiting cell wall synthesis targets. The chemical characterization, specific target, discovery process, along with the stage of development are provided here.

Methods: An extensive systematic search for NPs against the cell wall was performed considering all the articles published until the end of 2020 through the following scientific databases: NCBI PubMed, Scopus and Google Scholar and using the combination of the terms "natural antifungals" and "plant extracts" with "fungal cell wall".

Results: The first part of this review introduces the state of the art of the structure and biosynthesis of the fungal cell wall and considers exclusively those naturally produced GS antifungals that have given rise to both existing semisynthetic approved drugs and those derivatives currently in clinical trials. According to their chemical structure, natural GS inhibitors can be classified as 1) cyclic lipopeptides, 2) glycolipids and 3) acidic terpenoids. We also included nikkomycins and polyoxins, NPs that inhibit the CS, which have traditionally been considered good candidates for antifungal drug development but have finally been discarded after enduring unsuccessful clinical trials. Finally, the review focuses in the most recent findings about the growing field of plant-derived molecules and extracts that exhibit activity against the fungal cell wall. Thus, this search yielded sixteen articles, nine of which deal with pure compounds and seven with plant extracts or fractions with proven activity against the fungal cell wall. Regarding the mechanism of action, seven (44%) produced GS inhibition while five (31%) inhibited CS. Some of them (56%) interfered with other components of the cell wall. Most of the analyzed articles refer to tests carried out *in vitro* and therefore are in early stages of development.

Abbreviations: CS, chitin synthase; GPI, glycosylphosphatidylinositol; GS, β(1,3)-D-glucan synthase; NP, Natural product; PIR, proteins containing internal repeats; SEM, scanning electron microscopy; TEM, transmission electron microscopy; UDP-Glc, uridine-diphosphate-glucose; UDP-GlcNAc, uridine-diphosphate-N-acetylglucosamine.

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Conclusion: This report delivers an overview about both existing natural antifungals targeting GS and CS activities and their mechanisms of action. It also presents recent discoveries on natural products that may be used as starting points for the development of potential selective and non-toxic antifungal drugs.

Introduction

In the past three decades, the number of immunosuppressed patients affected by systemic fungal infections caused by species of *Aspergillus* and *Candida, Cryptococcus neoformans, Histoplasma capsulatum* and *Pneumocystis carinii* has dramatically increased (Cortés et al., 2019; Perfect, 2017; Vicente et al., 2003). Currently, four main classes of antifungal agents are used in patients with systemic mycoses: azoles (fluconazole, itraconazole, isavuconazole, posaconazole, and voriconazole) that block the biosynthesis of ergosterol by inhibiting the 14-α-demethylase, polyenes (conventional amphotericin B and its lipid formulations) that bind to the ergosterol of the fungal membrane, echinocandins (caspofungin, anidulafungin, and micafungin) that block the biosynthesis of the fungal cell wall β(1,3)-D-glucan by targeting the β(1,3)-D-glucan synthase (GS) and the pyrimidine analogues (5-flucytosine) that impede the synthesis of nucleic acids (Cortés et al., 2019; Perfect, 2017).

Natural products (NPs) and their semisynthetic derivatives have been traditionally an incomparable source of drugs to handle microbial infections. Accordingly, most clinical antimicrobials used today are derived from NPs (Roemer et al., 2011). However, while more than a dozen of clinically relevant antibacterial classes are naturally derived, only polyenes and echinocandins, among antifungals, are naturally produced, while azoles and pyrimidine analogues have a synthetic origin (Andriole, 1999; Roemer et al., 2011). The main reason for the low number of NPs classes developed into antifungal drugs is that fungal cells, as those of their human hosts, are eukaryotes and therefore, compounds that inhibit the synthesis of fungal proteins, DNA or RNA are likely to achieve the same effect in the patient, causing harmful secondary effects (Georgopapadakou and Walsh, 1994). Even approved antifungal drugs, such as polyenes, can hurt human cells by binding to cholesterol (Perfect, 2017).

Another reason is that before the 1970s fungal infections were easily treatable, and thus, the need for isolating new clinical antifungals at that time was reduced. During that period, antifungal treatment included exclusively two classes: potassium iodide and the polyenes nystatin and amphotericin B (Fig. 1). With the exception of the discovery of 5-flucytosine in the 1960s, there was not a real advance until the development of the azole class in the early 1970s (Perfect, 2017; Vicente et al., 2003). However, these antifungals have serious drawbacks due to their toxicity, low spectrum of activity and the emergence of strains resistant to them. Therefore, the discovery and clinical development of new antifungal agents, preferably those NPs exhibiting novel mechanisms of action, are an urgent need (Cortés et al., 2019; Perfect, 2017; Vicente et al., 2003).

The wall structure surrounding the cell is crucial for the survival of the fungus (**Fig. 2**). Importantly, this structure is lacking in human host cells, and consequently, antifungal drugs inhibiting the synthesis of the cell wall polysaccharides are generally less harmful than azoles or polyenes (Perfect, 2017). Therefore, the enzymes that synthesize essential cell wall polysaccharides, such as β(1,3)-D-glucan and chitin, are considered an extraordinary target for the discovery of new NPs with antifungal activity that later may serve as platforms to make new drugs (Cortés et al., 2019; Ribas et al., 2014; Roemer et al., 2011). In addition, it is interesting to note that, the newest classes of clinical antifungals that inhibit the GS (echinocandin and enfumafungin derivatives) or the traditional inhibitors of the chitin synthase (CS) (nikkomycins and polyoxins) are NPs obtained from fungi.

This review first describes the fundamentals of the fungal cell wall architecture and biosynthesis, to then discuss an anthology of the main NPs derived from microorganisms that have originated the established antifungal drugs currently used to treat invasive mycoses and that have the cell wall as target for their antifungal activity. Finally, we make emphasis in the latest research on the discovery, chemical characterization and development stage of plant extracts, fractions, and compounds capable of inhibiting the synthesis of the most important cell wall components.

Fungal cell wall fundamentals: composition and biosynthesis

The wall structure encasing the fungal cells grants the mechanical strength needed for protection against the internal osmotic pressure, that otherwise would cause cell lysis by pushing and breaking the plasma membrane (**Fig. 2**). However, the cell wall is not merely a rigid envelope, it must exhibit some elasticity for allowing its remodeling during the various morphogenesis processes that happen along the life cycle of the fungus, such as cell growth, cell separation or cell specialization (reviewed by Cortés et al., 2019; Ribas et al., 2014).

The cell wall is mainly comprised of polysaccharides (70-90%) and heavily glycosylated proteins (10-30%). Although composition varies between different fungal species, most walls exhibit a similar structure. Thus, transmission electron microscopy (TEM) shows two cell wall layers: the inner layer (less electrodense) contains a fibrillar network of β(1,3)-D-glucan, β(1,6)-D-glucan and chitin, with some species having also many fibrils of α(1,3)-D-glucan. The outer layer (more electrodense)

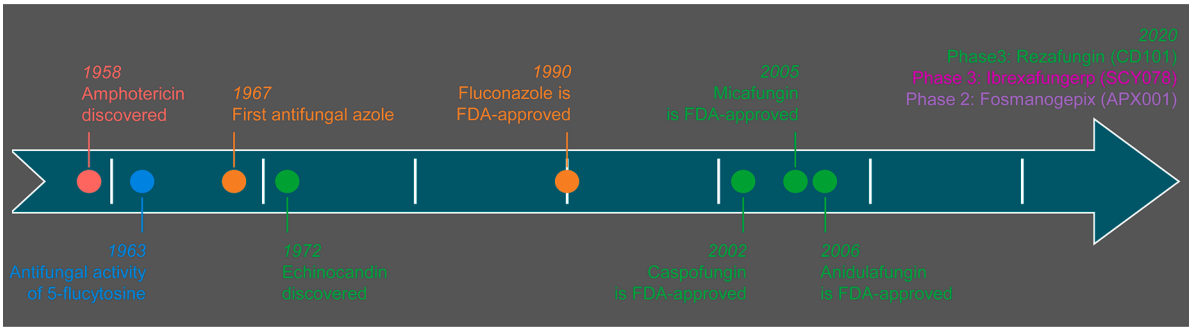


Fig. 1. Timeline showing major landmarks in the discovery and development of the four most important classes of antifungals utilized as a therapy for invasive fungal infections: the polyene amphotericin B (red), the pyrimidine analogue 5-flucytosine (blue), triazoles (orange) and echinocandins (green). The scheme also shows those compounds currently in clinical development: the echinocandin rezafungin (green), the enfumafungin-derivative ibrexafungerp (pink) and the inhibitor of the glycosylphosphatidylinositol synthesis fosmanogepix (purple).

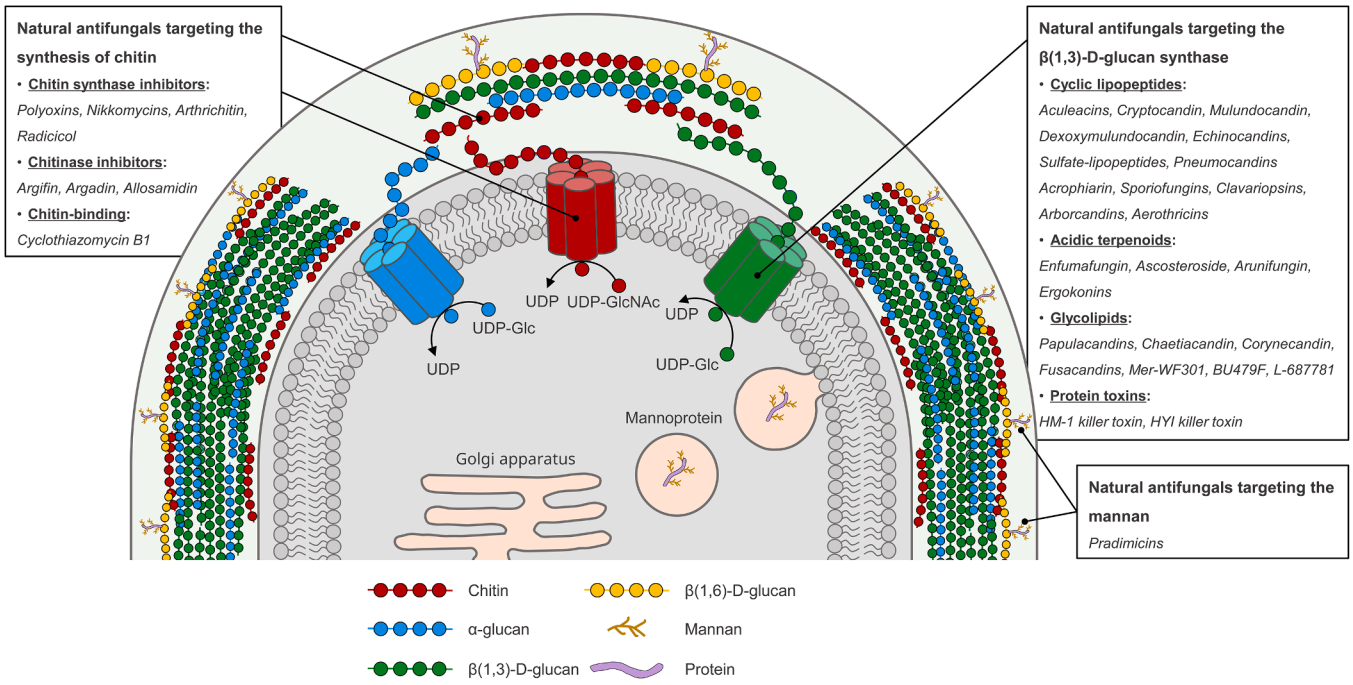


Fig. 2. Schematic representation of the assembly and structure of a typical fungal cell wall (adapted from Cabib and Arroyo, 2013). In most fungal species, the inner layer of the cell wall is composed of polysaccharides, such as β(1,3)-D-glucan, β(1,6)-D-glucan and chitin, with many species having also α-glucan. While β(1,3)-D-glucan, chitin and α-glucan are synthetized in the plasma membrane by integral membrane enzymes, the mechanism and location of β(1,6)-D-glucan synthesis is currently unknown. Mannoproteins are transferred in vesicles from the Golgi apparatus to the plasma membrane, and then attached to the outer layer of the cell wall. Well stablished natural antifungals targeting β(1,3)-D-glucan, chitin and mannan are also depicted.

is more variable between fungal species and includes the mannoproteins (**Fig. 2**) (reviewed by Cortés et al., 2019; Gow et al., 2017; Latge, 2007).

Except for the β(1,6)-D-glucan, whose location of synthesis is unknown, the linear chains of β(1,3)-D-glucan, chitin and α(1,3)-D-glucan are initially built at the plasma membrane by synthases and extruded to the periplasmic space (**Fig. 2**), where they later generate a tightly linked network responsible for the mechanical force of the cell wall (reviewed by Cabib and Arroyo, 2013; Gow et al., 2017).

β(1,3)-D-glucan

The β(1,3)-D-glucan embodies the 50 to 55% of the total cell wall polysaccharides in yeasts and reaches the 30% in filamentous fungi (Gastebois et al., 2009; Lipke and Ovalle, 1998; Orlean, 2012; Pérez et al., 2016). The cell wall glucans are mostly composed of glucose units connected through β(1,3) links (65-90%), although there are also some β(1,6), β(1,4), α(1,3) and α(1,4) glucans (see below). The chains of β(1,3)-D-glucan exhibit a worm-like coil conformation that confers flexibility and tensile strength to the cell wall. Normally, the β(1,3)-D-glucan is composed by a backbone of β(1,3)-D-glucan branched with lateral chains of β(1,6)-D-glucan (reviewed by Du et al., 2019; Klis et al., 2002; Lesage and Bussey, 2006).

In all known fungi the linear β(1,3)-D-glucan chains are synthesized by the enzyme complex GS, which is located in the plasma membrane (Cabib and Arroyo, 2013; Klis et al., 2002; Lesage and Bussey, 2006). Antifungals classes (**Fig. 2** and **Table 1**), such as cyclic lipopeptides (echinocandins), glycolipids (papulacandins) and acidic terpenoids (enfumafungin), inhibit the assembly of the β(1,3)-D-glucan by selectively targeting the enzyme GS in a non-competitive way (Douglas, 2001). The GS complex uses uridine-diphosphate-glucose (UDP-Glc) as substrate and catalyze the formation of linear β(1,3)-D-glucan chains (**Fig. 2**). The GS comprises at least two subunits: a regulatory GTP-binding subunit located in the cytosol and a catalytic subunit bound to the plasma membrane (Kang and Cabib, 1986; Kang et al., 1986). The GTPase Rho1 acts as the GS regulatory subunit (Arellano et al., 1996; Drgonova et al., 1996), while the family of integral membrane proteins Fks/Gls/Bgs functions as the GS catalytic subunits (reviewed by García Cortés et al., 2016; Gow et al., 2017; Pérez et al., 2016).

Once synthetized and branched with side chains of β(1,6)-D-glucan, the β(1,3)-D-glucan can be connected to other glucans, to chitin or to mannoproteins, delivering a great mechanical force to the wall, which is essential for maintaining the fungal cell integrity (Klis et al., 2002; Kollar et al., 1995; Kollar et al., 1997; Lesage and Bussey, 2006).

β(1,6)-D-glucan

The content of β(1,6)-D-glucan in the cell wall accounts from 5% to 21% depending on the fungal species (Klis et al., 1997; Lesage and Bussey, 2006; Lipke and Ovalle, 1998; Manners et al., 1973; Orlean, 2012). In contrast to the synthesis of the other glucans and chitin, the location and how is achieved the synthesis of β(1,6)-D-glucan are presently unknown (**Fig. 2**). The isolation of *KRE* mutants able to survive and grow in the presence of the K1 killer toxin, a protein that kills the yeast cells by primary attaching to the β(1,6)-D-glucan (Hutchins and Bussey, 1983), allowed the identification of several genes involved in the synthesis of β(1,6)-D-glucan in *Saccharomyces cerevisiae* and the corresponding paralogues in some pathogenic fungi (Aimanianda et al., 2009; Gilbert et al., 2010; Herrero et al., 2004; Page et al., 2003).

KRE genes have been also related to the production of β(1,3)-D-glucan, and the other way around, *FKS* genes in the production of β(1,6)-D-glucan (Dijkgraaf et al., 2002). The β(1,6)-D-glucan chains are shorter than those of the β(1,3)-D-glucan, and function as a cell wall adhesive that covalently interconnects to β(1,3)-D-glucan, chitin, and mannoproteins (Kollar et al., 1997).

Chitin

Chitin is a homopolymer composed of N-acetylglucosamine monomers linked through β(1,4) bonds. The enzyme chitin synthase (CS) use uridine-diphosphate-N-acetylglucosamine (UDP-GlcNAc) as substrate

Table 1
Natural inhibitors of the β(1,3)-D-glucan synthase activity isolated from fungi

Compound	Origin	Reference
Cyclic lipopeptides		
Hexapeptides		
Aculeacin A-G	*Aspergillus aculeatus*[a]	(Mizuno et al., 1977; Satoi et al., 1977)
Cryptocandin	*Cryptosporiopsis quercina*[b]	(Strobel et al., 1999)
Mulundocandin	*Aspergillus mulundensis*[c]	(Roy et al., 1987)
Deoxymulundocandin	*Aspergillus mulundensis*[c]	(Mukhopadhyay et al., 1992)
Echinocandins B-D	*Aspergillus. delacroxii*[d] *Aspergillus pachycristatus*[e] *Aspergillus nidulans*	(Benz et al., 1974; Hodges et al., 1994; Keller-Juslén et al., 1976; Traber et al., 1979)
Catechol-sulfate lipopeptides	*Coleophoma crateriformis* *Coleophoma empetri*[f] *Chalara sp.* *Phialophora cf. hyalina*[g]	(Hino et al., 2001; Iwamoto et al., 1994)
Pneumocandin A-E	*Glarea lozoyensis*[h] *Pezicula sp*[i] *Cryptosporiopsis sp*	(Morris et al., 1994; Noble et al., 1991; Schwartz et al., 1989; Schwartz et al., 1992)
Acrophiarin	*Penicillium arenicola*[j]	(Dreyfuss, 1986)
Sporiofungins A-C	*Pezicula radicicola*	(Dreyfuss, 1986)
Nonapeptide		
Clavariopsins A-B	*Clavariopsis aquatica*	(Kaida et al., 2001)
Decapeptide		
Arborcandins A-F	Filamentous fungus strain SANK 17397	(Ohyama et al., 2000)
Dodecapeptide		
Aerothricins	Fungal species No. 11243 Deuteromycotina spp	(Fujie et al., 2000a)
Acidic terpenoids		
Enfumafungin	*Hormonema carpetanum*	(Peláez et al., 2000)
Ascosteroside	*Ascotricha amphitricha* *Mycoleptodiscus atromaculans*	(Gorman et al., 1996; Vicente et al., 2001)
Arunifungin	*Arthrinium arundinis*[k] *Artrhrinium phaeospermum* *Coelomycete* undetermined *Leotiales anamorphs*	(Cabello et al., 2001)
Ergokonin A-C	*Trichoderma koningii* *Trichoderma viride* *Trichoderma longibrachiatum* *Fusarium sp LN-11* *Tolypocladium inflatum*	(Augustiniak et al., 1991; Grafe et al., 1991; Kumeda et al., 1994; Vicente et al., 2001; Yang et al., 2012)
Glycolipids		
Papulacandin A-E	*Papularia sphaerosperma*	(Traxler et al., 1977)
Chaetiacandin	*Monochaetia dimorphospora*	(Komori et al., 1985)
Corynecandin	*Coryneum modonium*	(Gunawardana et al., 1997)
Fusacandin A-B	*Fusarium sambucinum*	(Jackson et al., 1995)
Mer-WF301	*Phialophora cyclaminis*	(Kaneto et al., 1993)
BU479F	*Gilmaniella sp*	(Aoki et al., 1993)
L-687,781	*Dictyochaeta simplex*	(VanMiddlesworth et al., 1991)

[a] Formerly was considered as a variety of *Aspergillus japonicus* (Hamari et al., 1997)
[b] Imperfect stage of *Pezicula cinnamomea* (Strobel et al., 1999)
[c] Previously named as *Aspergillus sydowi var. mulundensis* (Bills et al., 2016)
[d] Previously named as *Aspergillus nidulans var. echinulatus* (Huttel et al., 2016)
[e] Previously named as *Aspergillus rugulosus* or *Aspergillus nidulans var. roseus* (Huttel et al., 2016)
[f] Synonym of *Coleophorma cylindrospora* (Crous and Groenewald, 2016)
[g] Previously identified as *Tolypocladium parasiticum,* synonym of *Pochonia parasitica* (Yue et al., 2015)
[h] Previously identified as *Zalerion arboricola* (Bills et al., 1999)
[i] Teleomorph state of the anamorph genus *Cryptosporiopsis* (Noble et al., 1991)
[j] Previously identified as *Acrophialophora limonispora* (Lan et al., 2020)
[k] Arthirium state of *Apiospora montagnei* (Cabello et al., 2001)

and catalyze the formation of linear microfibrils of chitin into the periplasmic space outside of the plasma membrane (**Fig. 2**). *S. cerevisiae* contains three CS activities (CSI, CSII, and CSIII), with the corresponding catalytic subunits being Chs1, Chs2 and Chs3, respectively (reviewed by Cabib et al., 2001; Roncero et al., 2016). Traditional antifungals (**Fig. 2**), such as the structural analogues of the UDP-GlcNAc, polyoxins and nikkomycins, are competitive inhibitors that block the CS activity by joining to catalytic site of the enzymes (Cabib, 1991).

Besides those genes described in the budding yeast, many other CS sequences have been found in over 200 fungal species. The number of CS genes identified per fungal species varies from two to nine, and considering the changes of their protein sequences, CSs have been grouped in two large families, subdivided in seven classes (Roncero et al., 2016). However, the diversity of CS enzymes suggests redundant functions of CS making complicated to find a functional differentiation between the seven classes (Lenardon et al., 2010).

Chitin comprises from 1 to 3% of the total cell wall polysaccharides in yeasts and ranges from 10 to 20% in molds (Bowman and Free, 2006; Kapteyn et al., 1997; Lesage and Bussey, 2006). Because of its rigidity, chitin is an important structural polysaccharide, being essential for cell wall organization and integrity, where it acts as a framework for the assembly of other wall components (Roncero et al., 2016).

Mannoproteins

The outer layer wall contains a large amount of proteins highly modified with carbohydrates both N- and O-linked, which are principally or entirely constituted by mannose units to form a polysaccharide known as mannan. Naturally produced pradimicins displays antifungal activity by binding to the wall mannan (**Fig. 2**). In *S. cerevisiae* and *Candida albicans* the layer of mannoproteins can reach up to 50% of the wall dry weight. Mannoproteins are linked through glycosylphosphatidylinositol (GPI) to the β(1,6)-D-glucan and the underlying fibrils of interconnected chitin-β(1,3)-D-glucan. In other cases, the β(1,3)-D-glucan is covalently bond to the external layer via proteins containing internal repeats (PIR) (Ecker et al., 2006; Mrsa et al., 1997; Mrsa and Tanner, 1999; Ruiz-Herrera et al., 2006).

The mannoproteins are modified with N-glycans, O-manno-oligosaccharides and a GPI remnant as they travel from endoplasmic reticulum to Golgi apparatus in the secretion route (**Fig. 2**). Initially, these structures are adhered to proteins in the luminal side of the endoplasmic reticulum and then, extended and modified in the Golgi to originate the mannoproteins, that finally will be either deposited in the plasma membrane or secreted to the periplasm and merged with other wall components (reviewed by Orlean, 2012).

One of the new antifungals currently in clinical trials (**Fig. 1**), APX001 (or fosmanogepix), blocks the incorporation of mannoproteins into the outer layer of the cell wall. This antifungal drug selectively inhibits the production of GPI by targeting the fungal Gwt1, an acyltransferase enzyme that is essential for GPI processing in the luminal membrane of the endoplasmic reticulum (Mutz and Roemer, 2016). Similarly, a search of synthetic or NP collections have detected additional compounds that target either Gwt1 or Mcd4, an ethanolamine phosphotransferase, which is also essential for the synthesis of GPI (Mann et al., 2015).

α(1,3)-D-glucan

Although this wall polysaccharide is not universally detected along the fungal kingdom, per example it lacks in budding yeasts such as *S. cerevisiae* or *C. albicans*, the internal wall layer of important fungal pathogens, such as *Aspergillus* spp., *C. neoformans* or *H. capsulatum* among others, contains fibrils of α(1,3)-D-glucan. In these fungi, the total content of this polysaccharide ranges from 28% to 46% (Grun et al., 2005; Henry et al., 2011; Pérez et al., 2016). In the fission yeast *Schizosaccharomyces pombe* this polymer exhibits two linear chains, each comprising approximately 120–130 monomers of glucose connected by α(1,3) bonds. The two chains are interconnected at the reducing ends by a bridge of about 10 units of α(1,4)-D-linked glucose (Grun et al., 2005).

As for the production of β(1,3)-D-glucan and chitin, the synthesis of α(1,3)-D-glucan has place in the plasma membrane (**Fig. 2**). The corresponding catalytic subunit contains a putative synthase domain located in the cytosolic side of the plasma membrane, multiple transmembrane domains and a transglycosylase domain situated in the periplasmic side of the plasma membrane (Vos et al., 2007). None α(1,3)-D-glucan synthase activity has been still detected *in vitro*. The first gene encoding for the α(1,3)-D-glucan synthase was found in the fission yeast, where it is essential for cell wall integrity and the yeast survival (Cortés et al., 2012; Hochstenbach et al., 1998; Katayama et al., 1999). In pathogenic fungi, the absence of genes encoding the α(1,3)-D-glucan synthase causes a reduction or loss of virulence (Beauvais et al., 2013; Edwards et al., 2011; Reese et al., 2007).

Natural antifungals targeting the cell wall

In this section, we will first specifically describe clinically well-established GS inhibitors or in an advanced step of development for the treatment of invasive fungal infections (cyclic lipopeptides and acidic terpenoids). We also described other natural inhibitors that exhibit a strong inhibitory activity against the GS (glycolipids) or CS

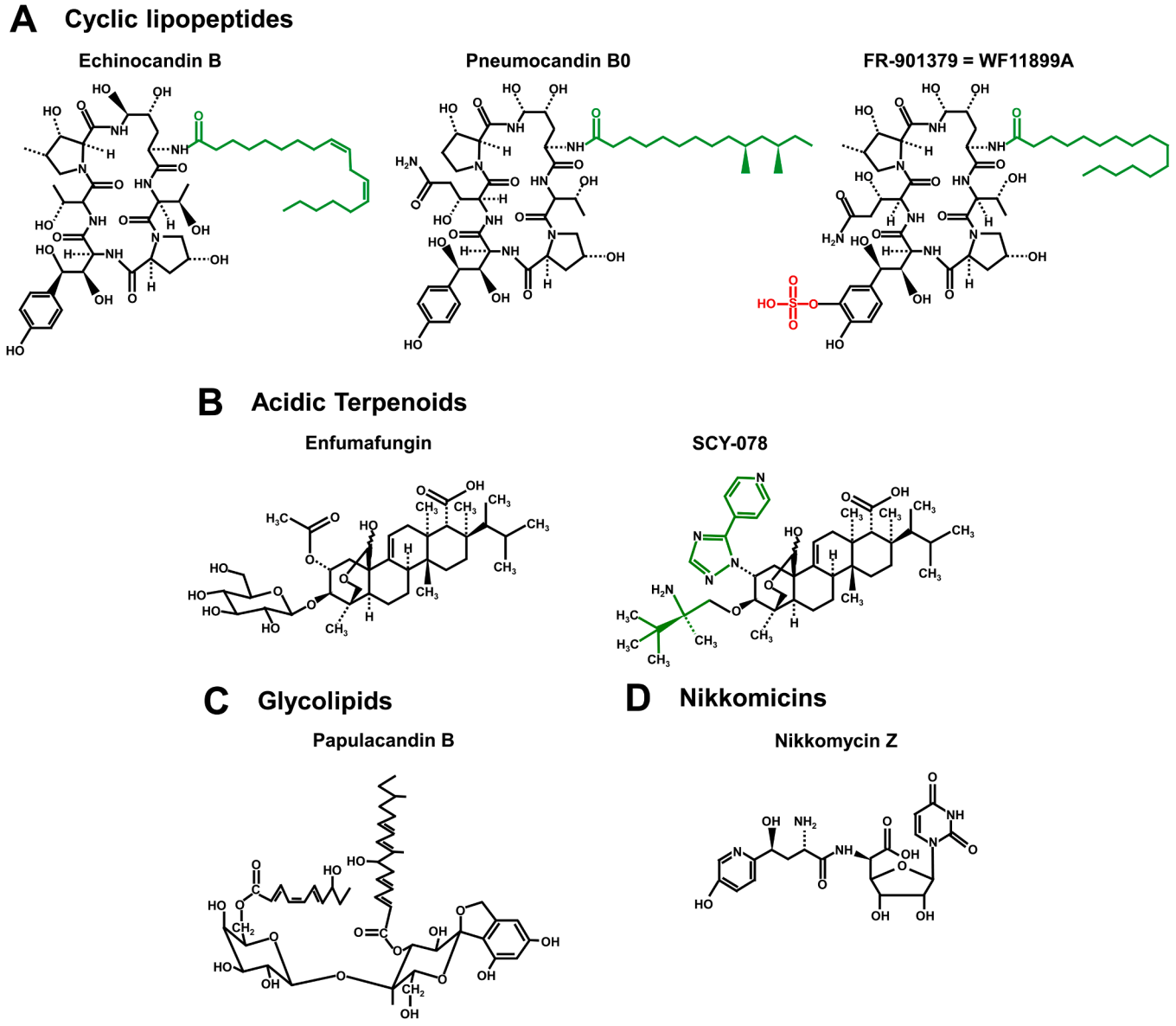


Fig. 3. Chemical structures of well-developed natural antifungals that block the synthesis of β(1,3)-D-glucan and chitin of the fungal cell wall. (A) Echinocandin B, pneumocandin B0 and FR-901379 are hexapeptides, precursors of the clinical echinocandins anidulafungin, micafungin and caspofungin, respectively. Alifatic side chains are represented in green and the sulfate ester in red. B) Enfumafungin is an acidic terpenoid forerunner of ibrexafungerp (SCY-078) which is currently in phase 3 of clinical development. Structural differences between natural enfumafungin and semisynthetic ibrexafungerp are depicted in green. C) Papulacandin B is a glicolipid. All of them inhibit β(1,3)-D-glucan synthesis. D) Nikkomycin Z is an inhibitor of chitin synthesis.

(polyoxins and nikkomycins) activities, but that have not been developed into antifungal drugs yet. For a more detailed revision of other naturally derived, semisynthetic, and synthetic antifungals that target the cell wall polysaccharides (**Fig. 2**), an interesting and comprehensive review has been recently published by (Liu et al., 2020). We will also detail the recent discoveries on NPs derived from plants that target the fungal cell wall. Although Phytomedicine is devoted to NPs coming from the vegetal kingdom, we included well-developed natural antifungals coming from fungi and bacteria to have an overview and to draw a perspective on the role played by the plant compounds in the development of new antifungal drugs targeting the fungal cell wall.

Existing natural β(1,3)-D-glucan synthase inhibitors

This class of antifungals blocks the biosynthesis of the fungal β(1,3)-D-glucan by inhibiting the GS enzyme (**Fig. 2**), which increases the osmotic sensitivity of the cells and cause cell lysis (Douglas et al., 1994; Pérez et al., 1981; Yamaguchi et al., 1985). This group of inhibitors is composed by several kinds of compounds not necessary chemically related. The three main classes are cyclic lipopeptides (echinocandins), acidic terpenoids (enfumafungins) and glycolipids (papulacandins). All of them are NPs derivatives that act non-competitively with the enzyme substrate UDP-Glc (Douglas, 2001; Perlin, 2019).

Cyclic lipopeptides

These compounds are non-ribosomal peptides, composed by a cyclic core containing a variable number of non-proteinogenic amino acids, and attached to a fatty acid side chain. The main group comprises the cyclic hexapeptides (**Table 1** and **Fig. 3A**), which are also known as echinocandin-like antifungals, or simply echinocandins, due to echinocandins comprise a specific type of hexapeptides (Wang et al., 2017). Echinocandins are fungicidal against *Candida* spp. and fungistatic against *Aspergillus* spp., (Patil and Majumdar, 2017) however, they are ineffective against *C. neoformans* (Cao et al., 2019).

Echinocandins are demonstrated to be non-competitive inhibitors of the GS, this is the reason why all of them are assumed to exert their antifungal activity via blockage of β(1,3)-D-glucan synthesis (**Fig. 2**) (Hawser et al., 2001; Kurtz and Douglas, 1997). Moreover, antifungals with a common mechanism of action lead to comparable effects at the proteome level (Bruneau et al., 2003). It seems that this inhibition requires the uptake of echinocandin molecules by sensitive cells. It is described that at concentrations of less than 1 mg/ml, a high-affinity facilitated-diffusion transporter mediates the uptake of caspofungin in *C. albicans*. On the other side, higher concentrations enter the cell in a non-specific way (Paderu et al., 2004). However, because the GS catalytic subunit is an integral membrane protein (**Fig. 2**), it continues unclear where echinocandins exactly attach to the GS (Denning, 2003; Odds et al., 2003). Thus, although it is clear that these inhibitors target the catalytic subunit of the GS, their inhibitory effects on β(1,3)-D-glucan synthesis might not involve the catalytic subunit itself (Odds et al., 2003). For example, it has been proposed that the acyl side chain of the echinocandins may insert into the plasma membrane (Chen et al., 2011). In agreement, inhibitors of the synthesis of the β(1,3)-D-glucan also decrease plasma membrane ergosterol and lanosterol (Pfaller et al., 1989).

Natural echinocandins cannot be used in clinical treatments due to their toxicity and low solubility. On the other hand, semisynthetic echinocandins, such as caspofungin, micafungin and anidulafungin, are clinically approved as the first-line treatment of some invasive mycoses (Balkovec et al., 2014; Cortés et al., 2019; Emri et al., 2013). Also, rezafungin, another semisynthetic echinocandin-derivative with improved physicochemical properties, is presently in advanced clinical development (**Fig. 1**). Besides echinocandins, fungi also produce cyclic nonapeptides, decapeptides and dodecapeptides exhibiting antifungal activity (**Table 1**) (Huttel, 2017; Yue et al., 2015).

Cyclic lipopeptides: Echinocandins

Echinocandins are effective against yeasts, especially *C. albicans,* causing rapid lysis in growing cells (Cassone et al., 1981). This class of antifungals was launched with the discovery of echinocandin B in the 1970s (**Fig. 1**, **Fig. 3A** and **Table 1**). This natural antifungal was widely studied in the next years due to its potent fungicidal properties. However, since echinocandin B also presented a strong hemolytic activity, it was necessary to develop some analogues by modification of its side chain to reduce its toxicity (Emri et al., 2013). As a result, cilofungin was the first echinocandin B-derivative candidate to be developed into a drug, but it was discarded because of its low solubility in water. Thus, some other modifications were carried out (Debono et al., 1995). Consequently, anidulafungin was later approved in 2006 (**Fig. 1**) as a clinical drug with superior solubility properties than those of echinocandin B and cilofungin (Ye et al., 2020). In addition, rezafungin, an anidulafungin derivative, is currently in phase 3 of clinical trials (Huttel, 2020). Finally, new semisynthetic analogs and new methodologies for respectively improving the physicochemical properties or the production of the echinocandin B nucleus have been recently described (Hu et al., 2020; Min et al., 2019; Niu et al., 2020; Shivakumar et al., 2019; Zhu et al., 2020).

Cyclic lipopeptides: Pneumocandins

Pneumocandins (A_0-A_4, B_0, B_2, C_0 and D_0) are acylated cyclic hexapeptides (**Fig. 3A** and **Table 1**). These NPs display a potent activity against *Candida* spp. and *P. carinii* (Adefarati et al., 1992; Morris et al., 1994; Schwartz et al., 1992). In 2002, caspofungin was the first echinocandin approved for clinical use in both the United States and the European Union (**Fig. 1**). This antifungal drug is a semisynthetic derivative of pneumocandin B_0 by insertion of supplementary amino groups in the hexapeptide nucleus. These modifications increased both the solubility of the molecule and the effectiveness against pathogenic yeasts. Caspofungin also has lower rates of nephrotoxicity, and drug-related adverse and infusion-related events (Denning, 2003; Emri et al., 2013; Sable et al., 2008; Vicente et al., 2003).

Cyclic lipopeptides: Catechol-sulfate lipopeptides

The main characteristic of this group is the presence of a sulphate ester at the cyclic hexapeptide nucleus (**Fig. 3A** and **Table 1**) which confers them excellent water solubility (Iwamoto et al., 1994). Like other echinocandins, sulfate lipopeptides present antifungal activities against *A. fumigatus* and *C. albicans* (Fujie et al., 2000b). In addition, they are effective against the human pathogen *Pneumocystis carinii* (Furuta et al., 1998). In spite of these good pharmacological properties, they also have hemolytic potential (Iwamoto et al., 1994), therefore they were used as start point for the development of new semisynthetic analogs, such as micafungin, which was generated from FR901379 (also named as WF11899A) by replacement of the fatty acid side chain with an aromatic complex (Tomishima et al., 1999) and approved for the treatment of candidemia in 2005 (**Fig. 1**) (Ye et al., 2020).

Cyclic lipopeptides: Other cyclic hexapeptides

In this section, we describe briefly other natural cyclic lipopeptides related to echinocandins that have shown to exhibit antifungal activity against diverse pathogenic fungi (**Table 1**). Aculeacins exhibit chemical and biological properties like those of echinocandin B (Mizuno et al., 1977). Aculeacin A is fungicide against the yeasts *Candida* spp. (except for *C. tropicalis*), *Saccharomyces* spp., *Mycotorula japonica* and *Torula utilis*. It also has a fungistatic effect on filamentous fungi, including *A. fumigatus*, dermatophytes and phytopathogenic fungi. Its nephrotoxicity in rats is lower than that of the polyene amphotericin B (Mizuno et al., 1977). In *S. cerevisiae* and *C. albicans*, aculeacin A acts selectively

on growing cells via inhibition of the β(1,3)-D-glucan synthesis (Ma et al., 2010). Aculeacins B to G show an antifungal spectrum very similar to that of aculeacin A, with aculeacin D showing the strongest activity against yeasts and aculeacin E against filamentous fungi (Satoi et al., 1977). Cryptocandin shows inhibitory activity against some human pathogens like *C. albicans* or *Trichophyton* spp. and some phytopathogenic fungi, so it was considered by some companies as a possible drug to treat fungal infections in skin and nails (Strobel, 2002). Acrophiarin is a pneumocandin variant which combines a hydroxy-glutamate typical of echinocandins in the fifth amino acid position of the cyclic hexapeptide with a straight myristoyl lateral chain (Lan et al., 2020). According to one patent from 1979, this echinocandin seems to be an effective antifungal molecule against several *Candida* spp. (Lan et al., 2020). Sporiofungins are echinocandin-like antifungals that exhibited a potent antifungal activity arresting the growth of *C. albicans* and other *Candida* spp. (Dreyfuss, 1986; Yue et al., 2018). Sporiofungins are like pneumocandins with L-serine instead L-threonine and 3-hydroxy-homotyrosine instead 3,4-dihydroxy-homotyrosine in the second and fourth amino acid positions, respectively (Yue et al., 2018).

Cyclic lipopeptides: Cyclic nonapeptides, decapeptides and dodecapeptides

Besides echinocandins, other antifungal cyclic lipopeptides containing rings with more than six amino acids are also naturally occurring (**Table 1**). Clavariopsins are cyclic nonapeptides that have also been proposed to inhibit the GS. These antibiotics display antifungal activity inhibiting *A. fumigatus, A. niger* and *C. albicans* (Kaida et al., 2001). Arborcandins are antifungal compounds with a nucleus containing ten amino acids and two side lipophilic tails. These decapeptides exhibit a potent non-competitive inhibition of the GS activity of *C. albicans* and, they are fungicidal against *C. albicans* and fungistatic against *A. fumigatus* (Ohyama et al., 2000). Finally, aerothricin (FR901469 or RO-09-3655) is a macrocyclic lipopeptidolactone comprising a ring with twelve amino acids and a 3-hydroxypalmitoyl lateral chain. This compound is interesting because has good solubility properties and inhibits the activity GS of *C. albicans* more efficiently than other GS inhibitors, such as aculeacin A, echinocandin B, WF11899 and papulacandin B (Fujie et al., 2000a).

Acidic terpenoids

Because the lack of oral bioavailability of echinocandins and the limited effectiveness in infected mice of papulacandins (see below), a search for new NPs allowed the identification of acidic terpenoids (enfumafungin, ascosteroside, arundifungin and ergokonin A) as a novel chemical class of GS inhibitors that could be engineered into new orally active drugs (**Fig. 2**, **Fig. 3B** and **Table 1**) (Onishi et al., 2000). These triterpenes comprise an acidic (polar) moiety that can be a glycoside in both ascosteroside and enfumafungin, a succinate in arundifungin or a sulphate-derivative amino acid in ergokonin A (Vicente et al., 2003). Like echinocandins, acidic terpenoids exhibit antifungal activity against species of *Aspergillus* and *Candida*, but are largely ineffective against *C. neoformans* (Cabello et al., 2001; Onishi et al., 2000; Peláez et al., 2000; Vicente et al., 2001). Although the acidic terpenoids are assumed to inhibit the GS, modified *in vitro* assays using *C. albicans* membranes showed that these NPs are much less effective (1000-fold) inhibiting the GS activity than caspofungin analogue L-733560 (Onishi et al., 2000).

Acidic terpenoids: Enfumafungin

The acidic terpenoid enfumafungin is a hemiacetal triterpene glycoside derivative obtained from the fermentation of the endophytic fungus *Hormonema carpetanum* (**Fig. 3B** and **Table 1**). The *in vitro* antifungal activity of enfumafungin is comparable to that of caspofungin analogues (Onishi et al., 2000; Peláez et al., 2000). Ibrexafungerp (SCY-078) is a semisynthetic derivative of enfumafungin, that is currently in phase 3 of clinical development (**Fig. 1** and **Fig. 3B**), and combines the improved safety profile of the echinocandins with the advantages of both oral and intravenous preparations (Apgar et al., 2020; Jiménez-Ortigosa et al., 2017; Kuhnert et al., 2018). Ibrexafungerp and other derivatives of enfumafungin are effective inhibitors of GS, yet these compounds seem to bind to different GS domains that echinocandins. Thus, Fks amino acid changes associated to echinocandin resistance are in some occasions different from those causing decreased sensibility to enfumafungin derivatives. Consequently, ibrexafungerp does not display cross resistance with echinocandins, and remains active against pathogens resistant to echinocandins (Jiménez-Ortigosa et al., 2017; Kuhnert et al., 2018). Ibrexafungerp also displays an outstanding *in vitro* activity against wild type and itraconazole-resistant isolates of *Aspergillus* and wild type species of *Candida* (Arendrup et al., 2020; Hector and Bierer, 2011; Pfaller et al., 2013a, b). In models of murine fungal infections, orally administered ibrexafungerp exhibited a wide range of antifungal activity against distinct species of *Candida* and *Aspergillus*, including *C. krusei* and strains resistant to echinocandins (Apgar et al., 2020).

Acidic terpenoids: Other acidic terpenoids

Three additional acidic terpenoids exhibiting antifungal properties have been isolated (**Table 1**). Ascosteroside is a glycoside of a lanostane type triterpenoid that shows activity against yeasts, such as *S. cerevisiae*, distinct *Candida* spp. and filamentous fungi. Mice infected with *C. albicans* and treated with ascosteroside exhibited a time of survival comparable to that of mice treated with ketoconazole (Gorman et al., 1996). Except for *C. glabrata,* ascosteroside exhibited less *in vitro* activity than enfumafungin against *Candida* spp. and *Aspergillus* spp. (Onishi et al., 2000). The acidic steroid arundifungin induced the same morphological phenotypes that echinocandins in growing hyphae of *A. fumigatus*. As the other acidic terpenoids, arundifungin inhibits the growth of *Candida* spp. and *Aspergillus* spp., although less effectively than enfumafungin (Cabello et al., 2001; Onishi et al., 2000). Highly oxygenated ergosterol derivative ergokonin A showed activity against *Candida* and *Aspergillus* spp., being ineffective against *Cryptococcus, Fusarium* and *Saccharomyces* (Vicente et al., 2001). Like ascosteroside and arundifungin, ergokonin A exhibited less antifungal activity than enfumafungin (Onishi et al., 2000). More recently, an improved screening for NPs targeting the cell wall identified a desulfated analogue of ergokonin A as a novel inhibitor of the β(1,3)-D-glucan synthesis, that might be active against *C. albicans* and/or *A. fumigatus* (Roemer et al., 2011).

Glycolipids

The papulacandins are glycolipids isolated from fungi that were first described in the 1970s (Traxler et al., 1977). Besides papulacandins, there are other fungal glycolipids exhibiting antifungal activity (**Table 1**). Except for chaetiacandin, all of them comprise a benzannulated spiroketal scaffold (**Fig. 3C**). Glycolipids generally show strong *in vitro* activity killing *Candida* spp. and several other yeasts, but they are ineffective against *C. neoformans* and *A. fumigatus* (Cortés et al., 2019). Because of their limited efficacy in animal models, no glycolipids have been approved as antifungal drugs (Vicente et al., 2003).

Glycolipids: Papulacandins

Like the echinocandin class, papulacandins inhibit the synthesis of the wall β(1,3)-D-glucan by selectively affecting the GS enzyme (**Fig. 2** and **Table 1**). Compared to other related glycolipids, papulacandin B exerts the most powerful inhibitory effect on the *in vitro* GS activity of *C. albicans* (Gunawardana et al., 1997). These glycolipids are very efficient and specific against several yeasts, but exhibit less effectiveness against filamentous fungi (Baguley et al., 1979; Font de Mora et al.,

1990; Pérez et al., 1983; Traxler et al., 1977; Varona et al., 1983). A comparative *in vitro* analysis showed that papulacandins are several orders of magnitude more effective than echinocandins and enfumafungin (see below) inhibiting the GS activity (Martins et al., 2011). Several papulacandin D derivatives have been synthesized by the modification of two partly unsaturated acyl chains linked to sugars (van der Kaaden et al., 2012). Also, an improved screening for the search of new NPs targeting the cell wall identified a new papulacandin analogue that could be effective against *C. albicans* and/or *A. fumigatus* (Roemer et al., 2011). Resistant mutants to papulacandin B have been identified in *S. cerevisiae* and *S. pombe* (Berzaghi et al., 2019; Castro et al., 1995; Martins et al., 2011; Ribas et al., 1991).

Glycolipids: Other natural glycolipids

Several other papulacandin-related natural antifungals have been reported (**Table 1**). Chaetiacandin is a natural glycolipid that was discovered through the search for inhibitors of fungal cell wall biosynthesis. Chaetiacandin has a high specific activity against yeasts, especially those mutants of *C. albicans* susceptible to polyoxins. On the other side, fungicidal activity of chaetiacandin against wild type *C. albicans* is like that of papulacandin B (Komori et al., 1985). Corynecandin contains an additional ester chain at position C3 and displays the same antifungal activity than other related glycolipids. However, it showed less effectiveness than papulacandin B inhibiting *in vitro* GS (Gunawardana et al., 1997). Other glycolipids are fusacandin A and B. Whereas the glycosidic part of fusacandin A is esterified with two chains of unsaturated fatty acids, fusacandin B is esterified exclusively with one fatty acid chain. Fusacandin A exhibited much more antifungal activity than fusacandin B. Fusacandin A activity was like that of papulacandin B against different species of *Candida, S. cerevisiae* and *A. niger*. Also, the effectiveness of fusacandin A inhibiting the *in vitro* GS activity was like that of the echinocandin cilofungin, but less than that of papulacandin B (Jackson et al., 1995). As other papulacandin-related glycolipids, Mer-WF301, BU-4794F and L-687,781 exhibit fungicidal activity against growing cells of *C. albicans*, but being inactive against *A. fumigatus* and *C. neoformans* (Aoki et al., 1993; Kaneto et al., 1993; VanMiddlesworth et al., 1991). Interestingly, doses of L-687,781 that exhibit low *in vivo* activity against *C. albicans*, were efficient against *P. carinii* (VanMiddlesworth et al., 1991).

Existing natural chitin synthase inhibitors

As β(1,3)-D-glucan, chitin is also essential for fungal cell wall integrity and absent in fungal hosts, therefore its synthesis seems an excellent target to develop new antifungal drugs (**Fig. 2**). NPs polyoxins and nikkomycins are inhibitors of the CS activity that were historically considered as promising molecules to progress into antifungal drug development. Sadly, none of these compounds had clinical development because of their reduced efficiency in infection models. This limited efficacy *in vivo* seems to be due to their weak bioavailability and the differential inhibition against the multiple families of CS isoenzymes found in fungi (Aimanianda and Latge, 2010; Debono and Gordee, 1994; Roncero et al., 2016).

Polyoxins and nikkomycins are peptidyl nucleoside antibiotics (**Fig. 3D**) which are naturally produced by bacteria of the genus *Streptomyces*. Because of their structural similarity with UDP-GlcNAc, these compounds are highly efficient inhibiting the CS activity by binding to the catalytic site of the Chs enzymes (Cabib, 1991). Polyoxin B exhibits the same activity than fluconazole against the pathogenic fungi *A. fumigatus, C. albicans* and *C. neoformans* (Liu et al., 2020). Polyoxins-related nikkomycin Z displays an extraordinary fungicidal activity against *Blastomyces dermatitidis, Coccidioides immitis* and *H. capsulatum* when administered orally to mice (Hector and Bierer, 2011), but it is less potent against *A. fumigatus*, and exhibits a fungistatic effect in *C. albicans* growth. Remarkably, caspofungin and nikkomycin Z are strongly synergic against *A. fumigatus* and *C. albicans* when combined together (Cortés et al., 2019; Fortwendel et al., 2009; Walker et al., 2008).

Recent findings on plant-derived antifungals as cell wall inhibitors

Medicinal plants have historically proven their value on its own and as a source of a wide variety of pure molecules with therapeutic potential (Arif et al., 2009). Plant-derived NPs possess a unique and vast chemical diversity that have shown the ability to form optimal interactions with biological macromolecules. Such structural diversity supports the belief that collections of NPs are not only more diverse than those made up of synthetic compounds, but that they better represent the "chemical space" of drug-like molecules (Wolfender and Queiroz, 2012). Over the years, numerous NPs have resulted in a significant number of drugs and drug candidates approved to treat many diseases (Wolfender and Queiroz, 2012). Thus, conventional medicine is increasingly receptive to the use of plant-derived drugs, as traditional antimicrobials become ineffective (Arif et al., 2009).

Here we report a review of extracts, fractions, and isolated compounds from higher plants with the most relevant activities targeting the main structural elements of the fungal cell wall. **Table 2** summarizes all plant derivatives, which will be detailed below, with demonstrated activity against the fungal cell wall published in recent years.

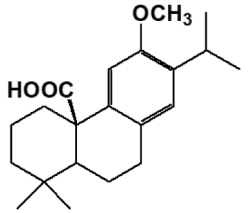
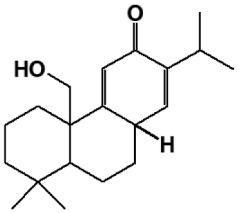
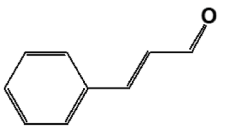
Plant-derived extracts and fractions that target the fungal cell wall

Punica granatum L. (Lythraceae) is a small, long-living tree cultivated throughout the Mediterranean region, as far north as the Himalayas, in Southeast Asia, and in California and Arizona in the United States. Ethanolic extracts prepared from the pericarp and from the peel of *P. granatum* fruit (**Table 2**) showed antifungal activity *in vitro* against *Candida* spp. (Anibal et al., 2013). When observed through both scanning electron microscopy (SEM) and TEM, the cells of *C. albicans* and *C. krusei* treated with *P. granatum* extracts appeared deformed and showed defects in cell separation. These defects could be probably due to the presence of both, a thick surrounding cell wall that seemed to be composed by multiple and denser layers, and an abnormal and thick septa between mother and daughter cells (Anibal et al., 2013). These authors suggest that tannins present in the extracts of *P. granatum* could be responsible for cell wall and septum changes in the species of *Candida*.

Tulbaghia violacea Harv. (Amaryllidaceae), commonly known as wild garlic, is a small bulbous herb used traditionally in the southern African region. Aqueous extracts from *T. violacea* bulbs (**Table 2**) showed antifungal activity *in vitro* against *Aspergillus flavus* (Belewa et al., 2011). TEM micrographs of spores exposed to the plant extract showed an induced remodeling of the spore cell wall (Somai and Belewa, 2011). It was also found that the extract caused a dose-dependent decrease of either the β-glucan content (62.5% at 12.5 mg/ml) or the GS activity (44.45% at 12.5 mg/ml) on *A. flavus*. Similarly, a reduction in the total content of chitin (83.34% at 12.5 mg/ml) corresponding to a decrease in CS activity in the presence of the plant extract (72.23% at 12.5 mg/ml) was also found. This inhibitory effect on the production of both β-glucan and chitin synthases results in the weakening of the *A. flavus* cell wall (Belewa et al., 2017). Thus, and unlike caspofungin or nikkomycin, this extract was able to inhibit both CS and GS activities, which are critical for maintaining the integrity of the fungal cell wall. As a consequence, the ability of the fungus to trigger a compensatory response to ensure cell wall integrity by increasing the production of β(1,3)-D-glucan or chitin is completely eliminated, limiting the fungus potential for developing resistance, and therefore making the extract an ideal candidate for its use as a possible antifungal agent (Belewa et al., 2017). Phytochemical analysis of the crude aqueous *T. violacea* extract indicated the presence of a high content of tannins, phenolics and saponins (Belewa et al., 2017).

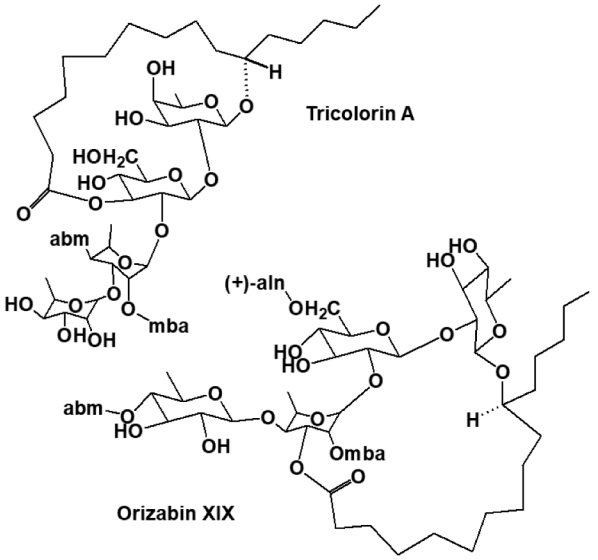
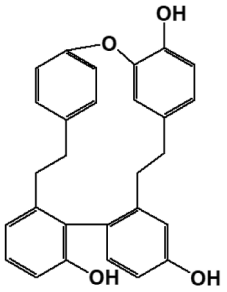
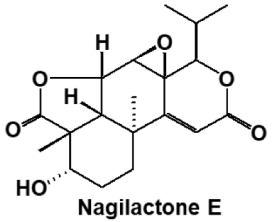
Aucklandia lappa DC. (Asteraceae), commonly known as costus or

Table 2
Natural antifungals from plants that target the fungal cell wall

Plant-derived extracts and fractions Plant species	Part used	Extract	Fraction	Effect on fungal cell wall	Reference
Aucklandia lappa DC. (Asteraceae)	Roots	Ethanolic		Decreases chitin content and inhibits GS (*Candida albicans*)	(Lee and Kim, 2020)
Camellia sinensis (L.) Kuntze (Theaceae)	Leaves	Methanol:H_2O (7:3)	Polyphenolic fraction rich in catechins and theaflavins	Release of celular content, production of shrunken cells (*C. albicans*)	(Sitheeque et al., 2009)
Phytolacca tetramera Hauman (Phytolaccaceae)	Berries	Dichloromethane		Deformed cells with defects in cell separation (*Schizosaccharomyces pombe, C. albicans*)	(Butassi et al., 2019b)
Plinia cauliflora (DC.) Kausel (Myrtaceae)	Leaves	Ethanol:H_2O (7:3)	Polyphenolic fraction rich in tannins	Denser outer layer of mannoproteins and reduced porosity (*C. albicans*)	(Souza-Moreira et al., 2013)
Punica granatum L. (Lythraceae)	Fruit (pericarp and peel)	Ethanolic		Deformed cells with defects in cell separation (*Candida* spp.)	(Anibal et al., 2013)
Tulbaghia violacea Harv. (Amaryllidaceae)	Bulbs (rhizomes)	Aqueous		Inhibits GS and CS (*Aspergillus flavus*)	(Belewa et al., 2011)
Zuccagnia punctata Cav. (Fabaceae) / *Larrea nitida* Cav. (Zygophyllaceae)	Aerial parts	Dichloromethane		Deformed cells with defects in cell separation. Inhibits GS and CS (*C. albicans*)	(Butassi et al., 2019a)
Plant-derived metabolites					
Plant source	**Part used**	**Extract**	**Compound / Chemical structure**	**Effect on fungal cell wall**	**Reference**
Chamaecyparis pisifera (Siebold & Zucc.) Endl. (Cupressaceae)	Leaves	Methanolic	 O-Methyl pisiferic acid	Inhibit CS (*S. cerevisiae, C. albicans*)	(Kang et al., 2008)
			 8,20-Dihydroxy-9(11), 13-abietadien-12-one		
Cinnamomum verum J.Presl (Lauraceae)	Bark	Essential oil	 *Trans*-cinnamaldehyde	Inhibits GS and CS and disrupt the β(1,3)-D-glucan layer (*S. cerevisiae, C. albicans*)	(Bang et al., 2000; Deng et al., 2018)

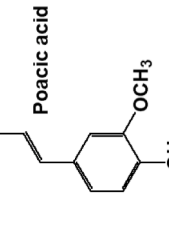
(*continued on next page*)

Table 2 (*continued*)

Plant-derived extracts and fractions Plant species	Part used	Extract	Fraction	Effect on fungal cell wall	Reference
Ipomoea tricolor Cav. and *Ipomoea orizabensis* (G. Pelletan) Ledeb. Ex Steud (Convolvulaceae)	Root	Chloroformic		Inhibits GS (*S. cerevisiae*)	(Castelli et al., 2002)
Marchantia polymorpha L. (Marchantiaceae)	Whole plant	Ethereal		Inhibits CS (*C. albicans*)	(Wu et al., 2008)
Podocarpus nagi (Thunb.) Pilg. (Podocarpaceae)	Root bark	Methanolic		Inhibits GS (*C. albicans, Aspergillus fumigatus*)	(Hayashi et al., 2018)
Raphanus sativus L. (Brassicaceae)	Seeds	Aqueous basic	**RsAFP2** (defensin, 51 amino acids, MW: 5.74 kDa)	Interacts with glucosylceramides producing abnormalities in the cell wall and aberrant budding (*C. albicans*)	(Thevissen et al., 2004)

(*continued on next page*)

Table 2 (*continued*)

Plant-derived extracts and fractions Plant species	Part used	Extract	Fraction	Effect on fungal cell wall	Reference
Rheum palmatum L., *Reynoutria japonica* Houtt., *Reynoutria multiflora* (Thunb.) Moldenke (Polygonaceae), *Aloe vera* (L.) Burm.f. (Xanthorrhoeaceae) and *Senna obtusifolia* (L.) H. S.Irwin & Barneby (Fabaceae)	Mainly in roots and rhizomes	Methanolic	 Emodin	Inhibits GS (*C. albicans*)	(Janeczko, 2018)
Spp. of the Poaceae family	Whole plant	Lignocellulosic hydrolysates (saponification)	 Poacic acid	It binds directly to the β(1,3)-D-glucan fibrils affecting the integrity and mechanical strength of the cell wall (*S. cerevisiae*)	(Piotrowski et al., 2015)

CS: chitin synthase; GS: β(1,3)-D-glucan synthase; MW: Molecular Weight

kuth, is a medicinal plant traditionally used in Korea, China, and India for treating digestive disorders (Li et al., 2005). Ethanolic extract from *A. lappa* roots (**Table 2**) showed antifungal activity against *Candida* spp. Fluorescence microscopy observation of *C. albicans* cells incubated with the extract revealed that cell wall becomes thinner through a reduction in chitin synthesis (Lee and Kim, 2020). In addition, the treatment causes the inhibition of the budding process and cell cycle arrest. Also, an aniline blue assay of membranes obtained from *C. albicans* cells treated with the extract showed an inhibition of the synthesis of β(1, 3)-D-glucan. Globally, these results suggested that *A. lappa* ethanolic extract affects cell wall integrity by decreasing chitin content and inhibiting β(1,3)-D-glucan synthase activity in *C. albicans* (Lee and Kim, 2020).

Phytolacca tetramera Hauman (Phytolaccaceae) is an endemic plant from Argentina. The dichloromethane extract from berries (**Table 2**) showed antifungal activity *in vitro* against *C. albicans*, and chemical analysis of this extract allowed the detection of two main monodesmosidic triterpenoid saponins: phytolaccoside B and phytolaccagenin, both with anti-candidal activity (Butassi et al., 2019a). *S. pombe and C. albicans* cells treated with *P. tetramera* extract appeared deformed and showed defects in cell separation when were observed through phase contrast and fluorescence microscopies, indicating a cell wall damage. Cellular and enzymatic GS and CS assays showed that this extract does not inhibit the activity of these cell wall enzymes, but it acts by binding to the ergosterol in the plasma membrane, causing a defect in cell wall synthesis and finally the cell death (Butassi et al., 2019a).

Zuccagnia punctata Cav. (Fabaceae) is an endemic plant from Argentina (Ulibarri, 2005) while *Larrea nitida* Cav. (Zygophyllaceae) is one of the four South American species of the genus *Larrea* (Timmermann et al., 1979) that grows in Argentina and Chile (Hunziker, 2005). In a previous work, a mixture of dichloromethane extracts from aerial parts of both plants showed synergism against *C. albicans* (Butassi et al., 2015). This mixture (**Table 2**), composed mainly of chalcones and lignans derived from nordihydroguayaretic acid, was studied according to its mechanism of action. The mixture acts by binding to ergosterol and producing a moderate dose-dependent inhibition of *C. albicans* GS and CS. Phase contrast and fluorescence microscopies revealed malformations in *S. pombe* cells treated with the mixture, suggesting that it acts in a dual way by binding to the membrane ergosterol and altering the fungal cell wall polymers (Butassi et al., 2019b).

Plinia cauliflora (DC.) Kausel (Myrtaceae) is a tree widespread in Brazil, Argentina, and Paraguay. A bioguided fractionation of the hydroalcoholic extract (70% ethanol) (**Table 2**) from *P. cauliflora* leaves against *Candida* spp. allowed to obtain a polyphenolic fraction rich in tannins. A preliminary phytochemical study led to detect casuarinin as the major component of this fraction (Souza-Moreira et al., 2013). The cell wall of *C. albicans* treated with this fraction was studied by TEM and was observed a denser outer layer of mannoproteins and a reduced cell wall porosity. Because tannins are known to complex with macromolecules such as proteins and polysaccharides (Haslam, 1996), the cell wall changes caused by the fraction may be due to the formation of a tannin-mannoproteins complex in the outer layer of *C. albicans* cell wall (Souza-Moreira et al., 2013).

Camellia sinensis (L.) Kuntze (Theacea) (tea plant) is a shrub that comes from Southern China and Southeast Asia, although today it is cultivated around the world, both in tropical and subtropical regions. The polyphenols catechins and theaflavins present in the hydroalcoholic extract (70% methanol) of this plant have shown many medicinal properties including antifungal activity. These tea polyphenols (**Table 2**) inhibited the growth of *C. albicans in vitro* (Sitheeque et al., 2009). SEM observation of *C. albicans* cells exposed to both catechins and theaflavins showed a release of cellular contents, indicative of death by cell lysis, and the production of shrunken cells. Some yeast cells showed a “mulberry-like” surface that is likely to be a transitional phase between the normal to the collapsed cell wall stage. These results

revealed considerable cell wall damage of *C. albicans* cells exposed to the polyphenols (Sitheeque et al., 2009). These compounds, like tannins, can form complexes with macromolecules (Haslam, 1996), which would explain its action on the cell wall.

Plant-derived compounds that target the fungal cell wall

RsAFP2 (**Table 2**) is an antifungal cysteine-rich peptide (known as defensin) isolated from seeds of *Raphanus sativus* L. (Brassicaceae) (Terras et al., 1992). This compound was active *in vitro* against different isolates of *Candida* spp. (Tavares et al., 2008) and it was also effective *in vivo* in a prophylactic murine model of candidiasis caused by *C. albicans* (Tavares et al., 2008). In *C. albicans,* RsAFP2 interacts primarily with the glucosylceramide, a plasma membrane sphingolipid that has been also proposed to be found in the proteinaceous fraction of the cell wall (Thevissen et al., 2012). RsAFP2 antifungal activity induces cell wall abnormalities and aberrant budding, without the need to be taken up intracellularly. This compound also activates the cell wall integrity pathway, which is one of the MAPK pathways known to be activated under conditions that perturbate either the cell wall or the plasma membrane in *C. albicans* (Thevissen et al., 2012). Since the glucosylceramide is (i) produced by most fungal pathogens (Barreto-Bergter et al., 2004), (ii) required for virulence in *C. albicans* (Noble et al., 2010), and (iii) not structurally related to the human glucosylceramide, the defensin RsAFP2 could exhibit a selective antifungal activity, and thus it could be used as a starting point for the discovery and development of a new family of antifungals drugs (Thevissen et al., 2004).

Poacic acid (**Table 2**) is a decarboxylated product from 8-5-diferulic acid commonly found in lignocellulosic hydrolysates of Poaceae family. This compound binds directly to β(1,3)-D-glucan fibrils of *S. cerevisiae* cell wall and rapidly produces a disruption of cell wall integrity, leading to cell lysis when the cell turgor pressure bursts the plasma membrane under a weakened cell wall (Piotrowski et al., 2015). It has been proposed that poacic acid specifically binds to the nascent linear chains of β(1,3)-D-glucan, affecting the posterior maturation of the polysaccharide and thus, the integrity and the mechanical strength of the cell wall (Lee et al., 2018). This mode of action is distinct from the one exhibited by echinocandins, acidic terpenoids and papulacandins (see above), which specifically block the synthesis of β(1,3)-D-glucan by inhibiting the activity of the GS. The fact that poacic acid shows a synergistic effect with caspofungin, would confirm that these compounds target the cell wall through different mechanisms. Poacic acid is also synergic with fluconazole (Piotrowski et al., 2015).

The phenolic macrocyclic *bis*(bibenzyl), plagiochin E (**Table 2**), isolated from the Chinese liverwort *Marchantia polymorpha* L. (Marchantiaceae) was found to have antifungal activity *in vitro* against *C. albicans* (Niu et al., 2006). TEM observation of *C. albicans* cells treated with this compound showed an extremely damaged cell wall structure, suggesting that the antifungal activity of plagiochin E could be associated with its effect on the cell wall (Wu et al., 2008). Plagiochin E produced a dose-dependent inhibitory effect against *C. albicans* CS (Chs1, Chs2 and Chs3) *in vitro*. The effect of plagiochin E on *in situ* chitin synthesis was also determined during spheroplast regeneration of *C. albicans*, also showing inhibition of chitin synthesis (Wu et al., 2008). Furthermore, plagiochin E also altered the expression of several CS genes in *C. albicans*, where the transcripts of *CHS1* were significantly decreased, while the expression of *CHS2* and *CHS3* was upregulated (Wu et al., 2008).

Emodin (6-methyl-1,3,8-trihydroxyanthraquinone, **Table 2**) is a natural anthraquinone derivative found mainly in the roots and rhizomes of numerous plants including *Rheum palmatum* L., *Reynoutria japonica* Houtt., *Reynoutria multiflora* (Thunb.) Moldenke (Polygonaceae), *Aloe vera* (L.) Burm.f. (Xanthorrhoeaceae), *Senna obtusifolia* (L.) H. S. Irwin & Barneby (Fabaceae). This compound reduced the *C. albicans* GS activity, leading to the disruption of β(1,3)-D-glucans in the fungal cell wall and increasing cell wall damage (Janeczko, 2018).

Nagilactones are norditerpene dilactones isolated from the root bark of *Podocarpus nagi* (Thunb.) Pilg. (Podocarpaceae), an evergreen tree that grows mainly in western Japan (Hayashi et al., 2018). Among them, nagilactone E (**Table 2**) has been reported to induce morphological changes in *S. cerevisiae* cells, such as inhomogeneous thickness of the glucan layer and leakage of cytoplasm. These phenotypes were accompanied by a reduction of the *in vitro* GS activity. Furthermore, nagilactone E induced the swelling of *A. fumigatus* hyphae, suggesting that this compound weakens the cell wall of this pathogenic fungus (Hayashi et al., 2018).

The phenyl aldehyde *trans*-cinnamaldehyde (**Table 2**) is the main component of *Cinnamomum verum* J. Presl (Lauraceae) bark essential oil. *In vitro* studies with this compound showed a noncompetitive and mixed inhibitory effect on *S. cerevisiae* GS and CS, respectively (Bang et al., 2000). Additionally, the effect of this compound was studied *in vivo* using an immunosuppressed mouse model with invasive pulmonary candidiasis. TEM observation indicated that β(1,3)-D-glucans layer of the cell wall of *C. albicans* was rough, deformed, and incomplete, without affecting the cell membrane (Deng et al., 2018).

The compounds with diterpene skeleton *O*-methyl pisiferic acid and 8,20-dihydroxy-9(11),13-abietadien-12-one (**Table 2**), isolated from the leaves of *Chamaecyparis pisifera* (Siebold & Zucc.) Endl. (Cupressaceae) were evaluated as inhibitors of the three *S. cerevisiae* CS. *O*-methyl pisiferic acid strongly inhibited Chs2 in a dose-dependent manner, whereas 8,20-dihydroxy-9(11),13-abietadien-12-one showed a very weak inhibitory activity. These compounds showed no effects on Chs3 activity, whereas they exhibited very weak inhibitory activities on Chs1. *O*-methyl pisiferic acid also inhibited Chs1 of *C. albicans* (*S. cerevisiae* Chs2 analog), indicating that it is a specific inhibitor of Chs2. Kinetic analysis of inhibition demonstrated that *O*-methyl pisiferic acid acts as a mixed type competitive inhibitor with respect to the substrate UDP-GlcNAc (Kang et al., 2008).

A series of sixteen related glycolipids, tricolorins and orizabins, isolated from the chloroformic root extracts of two members of the Convolvulaceae family, *Ipomoea tricolor* Cav. and *Ipomoea orizabensis* (G. Pelletan) Ledeb. Ex Steud (Bah and Pereda-Miranda, 1997; Hernández-Carlos et al., 1999; Pereda-Miranda and Hernández-Carlos, 2002), were evaluated for their inhibitory activity of *S. cerevisiae* GS (Castelli et al., 2002). Most glycolipids tested were strong *in vitro* inhibitors with IC_{50} values comparable to that of papulacandin B. The compounds that showed the greatest inhibitory potential on the GS enzymatic activity within each series were tricolorin A and orizabin XIX (Table 2).

Conclusions and perspectives

Semisynthetic echinocandins are currently the main treatment against some fungal infections. This review provides an overview about new and old classes of cell wall-targeting fungal and bacterial derived antifungals and their mode of action, offering alternative natural compounds that might be employed as platforms for engineering new derivatives with better physicochemical properties that can be developed into antifungal drugs.

On the other side, the interest of NPs obtained from medicinal plants as a source of a wide variety of secondary metabolites with antifungal properties has increased in the last years (Perumal Samy and Gopalakrishnakone, 2010). The plant extracts, fractions and compounds isolated from them that target the cell wall presented in this review represent a promising alternative for the search for novel antifungal agents. Among the compounds present in the analyzed plants, we mainly find tannins (such as casuarinin, punicalagin and galladydilacton), polyphenols (catechins and theaflavins), phenolics (poacic acid and plagiochin E), flavonoids (chalcones), lignans (nordihydroguayaretic acid), glycolipids (tricolorins and orizabins), anthraquinones (emodin), peptides (defensin), triterpenoid saponins (phytolaccoside B and its genin phytolaccagenin), diterpenes (*O*-methyl pisiferic acid and 8,

20-dihydroxy-9(11),13-abietadien-12-one) and diterpenic lactones (nagilactone E), many of which have reported antifungal activity, being their main target the cell wall (Perumal Samy and Gopalakrishnakone, 2010). Many of these plant-derived antifungals, inhibit enzymes involved in the synthesis of the main cell wall polymers (GS, CS or both), and others bind polysaccharides (β(1,3)-D-glucan or chitin) or other molecules that are part of its architecture (mannoproteins and glucosylceramides), causing a defect in the synthesis.

Globally, these findings encourage the development of new antifungals with different mechanisms of action than those currently in clinical use. As the cell wall is critical for fungal growth and development, and is absent in human cells, these plant-derived antifungals are interesting for future development of selective drugs targeting the fungal cell wall as alternatives with fewer adverse effects.

Declaration of Competing Interest

M.A.C., E.B., J.C.R, L.A.S. and J.C.G.C. declare that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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