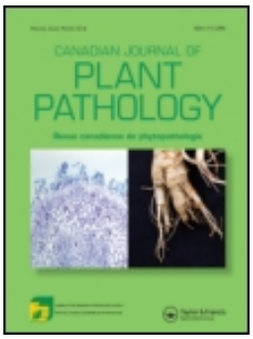

Canadian Journal of Plant Pathology

ISSN: 0706-0661 (Print) 1715-2992 (Online) Journal homepage: informahealthcare.com/journals/tcjp20

Antifungal compounds that target fungal membranes: applications in plant disease control

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To cite this article: T.J. Avis (2007) Antifungal compounds that target fungal membranes: applications in plant disease control, Canadian Journal of Plant Pathology, 29:4, 323-329, DOI: 10.1080/07060660709507478

To link to this article: https://doi.org/10.1080/07060660709507478

Minireview / Minisynthèse

Antifungal compounds that target fungal membranes: applications in plant disease control

T.J. Avis

Abstract: The fungal membrane has the fundamental role of maintaining cell order and integrity. Therefore, a number of disease-control methods have involved compounds that directly or indirectly target fungal membranes or their components. Some of these antifungal compounds affect the synthesis of specific membrane components (e.g., sterol biosynthesis inhibitors) and are among the most effective antifungals in plant disease control. However, these compounds are prone to pathogen resistance development that greatly shortens their effective life span. Conversely, some antifungals possess generalized effects on fungal membrane integrity. These compounds are typically not as effective, but they are less likely to induce resistance in sensitive fungi. The use of both classes of antifungals is still of great relevance in plant pathology, in particular in the case of integrated pest management. The correct use of antifungals that target fungal membranes could be the basis of a promising strategy to lower applications of synthetic pesticides while lengthening the effective life span of the disease control measure.

Key words: antifungal fatty acid, antifungal salt, antimicrobial peptide, choline synthesis inhibitor, disease control, fungal membrane, saponin, sterol biosynthesis inhibitor.

Résumé : La membrane fongique joue le rôle fondamental du maintien de l'ordre et de l'intégrité de la cellule. Ainsi, de nombreuses méthodes de lutte contre les maladies impliquent des composés qui ciblent directement ou indirectement les membranes fongiques ou leurs composantes. Certains de ces composés antifongiques affectent la synthèse de composantes membranaires spécifiques (e.g., inhibiteurs de la synthèse des stérols) et sont parmi les composés antifongiques les plus efficaces dans la lutte contre les maladies des plantes. Par contre, ces composés sont vulnérables au développement de résistance chez les champignons ciblés, ce qui réduit considérablement leur durée de vie efficace. En revanche, d'autres composés antifongiques possèdent des effets généralisés sur l'intégrité membranaire. Ces composés sont typiquement moins efficaces, mais sont moins propices au développement de résistance chez les champignons sensibles. L'usage de ces deux classes de composés antifongiques demeure d'une grande pertinence en pathologie végétale, particulièrement dans un contexte de lutte intégrée. L'usage approprié de composés antifongiques affectant les membranes pourrait être à la base d'une stratégie prometteuse destinée à réduire les applications de pesticides de synthèse tout en allongeant leur durée de vie efficace dans la lutte contre les maladies des plantes.

Mots-clés : acide gras antifongique, sel antifongique, peptide antimicrobien, inhibiteur de la synthèse de la choline, lutte contre les maladies, membrane fongique, saponine, inhibiteur de la synthèse des stérols.

Introduction

Fungi are quantitatively the most important group of plant pathogens in contrast to animal pathogens, which are mostly bacterial or viral in nature. Consequently, the greatest advances in fungal disease control come from phytopathological studies, whereas fewer examples appear in medicine (Bryskier 2005). In an attempt to control fungal plant diseases, numerous chemical, genetic, biological, and other methods have been developed with varying short- and long-term efficacy. A number of these disease-control methods involve compounds that directly or indirectly target fungal membranes. This is not surprising because the fungal membrane is responsible for many essential cell functions, and its integrity is paramount to the survival of the fungus (Deacon 2006).

This review outlines the principal modes of action of compounds that target fungal plant pathogen membrane components, including newer antifungal classes from the most recent literature. These compounds may be synthetic fungicides or antifungal metabolites produced by antagonists (biocontrol agents) or by the host plant as part of its

Accepted 25 October 2007.

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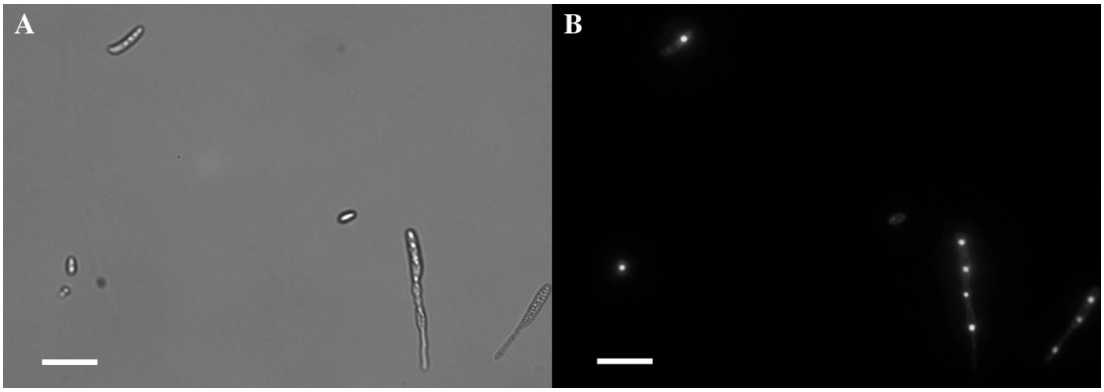
Published online 01 Apr 2010

Fig. 1. Visualization of micro- and macro-conidia of *Fusarium sambucinum* exposed to an antifungal salt (sodium metabisulfite) that targets cell membranes. The fluorescent stain (SYTOX green nucleic acid stain) does not cross intact plasma membranes but readily penetrates damaged ones and binds to nucleic acids, where it induces a fluorescence emission under blue light. (A) Conidia under visible light; (B) conidia under blue light (488 nm). Scale bars = 10 μm.



natural defense mechanisms. This paper will also shed light into the specificity and various applications of these antifungal compounds based on their mode of action and on the intrinsic membrane composition of fungal pathogens. Finally, the review will attempt to clarify the implications of disease control through the use of compounds that target fungal membranes.

The fungal membrane

Fungal membranes are the second structure encountered by an antifungal compound after the cell wall. Fungal membranes are similar to those of most eukaryotes, although they do have some unique constituents and important compositional differences that lead to sensitivity, insensitivity, tolerance, or resistance in fungi based on the nature and mode of action of the antifungal compounds.

Fungal membrane constituents and structure

Most fungal membrane constituents and their three-dimensional disposition are akin to those of other eukaryotic cell. Therefore, fungal membranes consist of a fluid mosaic comprised of a phospholipid bilayer with associated transmembrane proteins and enzymes. As in most eukaryotes, phosphatidylcholine and phosphatidylethanolamine are the major phospholipid moieties in fungal membranes (Weete 1974), and these phospholipids contain fatty acyl chains of varying lengths and unsaturation. Fungal membranes do differ in one important respect from other eukaryote cell membranes: their sterols. Specifically, fungal membranes typically contain ergosterol (a 28-carbon sterol; C_{28}) as the main sterol (Bloch 1983) in contrast to animals, whose membranes contain cholesterol (C_{27}), and plants, whose membranes contain phytosterols (C_{29}) such as sitosterol and stigmasterol. Some members of Oomycota also contain plantlike sterols (Deacon 2006). Of particular interest in the case of disease control, *Pythium* and *Phytophthora* spp. (kingdom Straminipila) are plant-pathogenic fungus-like organisms that are unable to synthesize sterols from nonsterol precursors and need sterols supplied by the host plant to "spark" some biological functions, such as sexual reproduction. The lack of sterols in these genera has practical implications in the use of antifungal compounds as will be discussed below.

The primordial role of fungal membranes

The fungal membrane has many important functional roles for the cell (Deacon 2006). The membrane is directly or indirectly involved (i) in nutrient uptake, (ii) in anchoring integral membrane proteins and enzymes, and (iii) in relaying signals from the external environment to the cell interior (signal transduction). Among all the roles that the fungal membrane plays, the most important is probably its general function of keeping cell order and integrity. When the order in fungal membranes is excessively disrupted, other fundamental membrane-associated functions, e.g., membrane protein and enzyme conformation and activity, is modified or lost. When membrane disorder becomes too great, a loss in membrane permeability (integrity) may ensue (Fig. 1), causing the release of intracellular components and, eventually, cell death (Avis and Bélanger 2001).

Antifungal agents that target fungal membranes

For the purpose of this review, antifungal compounds have been classified based on their mode of action. Although the list of antifungal compounds is not comprehensive, each example is meant to provide the general characteristics of compounds possessing equivalent modes of action. Particularities in these modes of action have been highlighted so as to emphasize the relative sensitivity of fungal pathogens based on intrinsic membrane components and current or foreseen applications in plant pathology are given.

Compounds affecting synthesis of specific membrane components

This section will review antifungal compounds affecting the synthesis of two of the major components in fungal membranes: sterols and phospholipids. These compounds include one of the most widely used antifungal classes in plant pathology as well as newer compounds that find specific applications.

Table 1. Site of action of ergosterol biosynthesis inhibitors.

Step in ergosterol biosynthesis*	Enzyme	Inhibitor (SBI class)
Squalene to 2,3-oxidosqualene	Squalene epoxidase	Thiocarbamates (class IV)
2,3-Oxidosqualene to lanosterol	Lanosterol synthase	
Lanosterol to zymosterol (two intermediate steps)	Lanosterol (C-14) demethylase	DMI fungicides (class I)
	C-14 sterol reductase	Amines (class II)
	C-4 sterol demethylase enzymes	Hydroxyanilides (class III)
Zymosterol to fecosterol	C-24 sterol methyltransferase	
Fecosterol to episterol	C-8 sterol isomerase	Amines (class II)
Episterol to ergosterol (two intermediate steps)	C-5 sterol desaturase	
	C-22 sterol desaturase	
	C-24 sterol reductase	

Note: The information in the table is adapted from White et al. (1998). SBI, sterol biosynthesis inhibitors; DMI, demethylation inhibitor.

*Several intermediates, side paths, and alternate pathways are not listed for simplification.

Compounds affecting sterol biosynthesis

Probably the most well-known and frequently used antifungal compounds that target membrane constituents are sterol biosynthesis inhibitors (SBI). This class of compounds includes demethylation inhibitor (DMI) fungicides (imidazoles, triazoles, piperazines, pyridines, and pyrimidines), amines (morpholines, piperidines, and spiroketalamines), hydroxyanilides, and thiocarbamates that block various steps of ergosterol biosynthesis in fungi (Table 1). The ensuing loss in ergosterol is of capital importance: among other roles, ergosterol stabilizes the physical properties of the membrane and provides the correct fluidity to ensure the membrane's barrier effect as well as correct membrane protein function (Avis and Bélanger 2001; Bryskier 2005).

Ergosterol biosynthesis inhibitors have generally been used as efficient, broad-spectrum fungicides for controlling a wide variety of fungal pathogens. However, an exception to efficient control of diseases by SBI is the case of Pythiaceous fungus-like organisms (*Pythium* and *Phytophthora* spp.). It is generally accepted that Pythiaceous genera lack the ability to synthesize sterols (including ergosterol), although some isolated reports to the contrary do exist (e.g., Trigos et al. 2005). Therefore, the relative insensitivity of Pythiaceous organisms to SBI is based on the lack of an intrinsic sterol biosynthetic pathway that is the site of action of SBI fungicides and should not be confused with resistance of these genera through mutations in target sites of action.

Compounds affecting phospholipid biosynthesis

Phospholipids are the backbone of the membrane's fluidic bilayer. Among the phospholipids found in fungal membranes, phosphatidylcholine is generally the most abundant and has been used as the target of antifungal compounds. Phospholipid biosynthesis inhibitors are a class of antifungal compounds that include (i) choline biosynthesis inhibitors (phosphorothiolates and dithiolanes) and, possibly, (ii) carboxylic acid amides (cinnamic acid amides, valinamide carbamates, and mandelic acid amides), although the exact mode of action of the latter class is not clear.

Choline biosynthesis inhibitors (CBI) interfere with methyltransferase activity in the transmethylation of ethanolamine to choline in the biosynthesis of phosphatidylcholine through Kennedy's pathway (Uesugi 2001). The ensuing loss of phosphatidylcholine has been shown to cause disorganization of the fungal cell membrane accompanied by leakage of cytoplasmic substances (Kodama et al. 1979, 1980). In particular, *Magnaporthe grisea* (Hebert) Yaegashi & Udagawa (rice blast) has shown high sensitivity to CBI, whereas the effectiveness of CBI against other rice pathogens has been less apparent. It has been proposed that *M. grisea* is more sensitive to CBI, because its principal route of phosphatidylcholine biosynthesis is Kennedy's pathway (Yoshida et al. 1984). Plant pathogenic fungi with a principal route of direct transmethylation of phosphatidylethanolamine to phosphatidylcholine (Greenberg's pathway) are less sensitive to CBI because these antifungals are not known to inhibit this pathway (Uesugi 2001).

Compounds with generalized effects on fungal membrane integrity

This section will describe the mode of action and (potential) applications of antifungal compounds that interact with fungal membranes rather than the synthesis of membrane components. These compounds disorganize and disrupt membrane order, integrity, and permeability through (i) binding to membrane components and (or) producing pores, (ii) affecting the general membrane lipid domain, or (iii) other mechanisms involving the modification or damage of membrane components. Regardless of their specific mode of action, these compounds can have dramatic effects on the viability of fungal cells that have proven or potential applications in plant disease control.

Compounds that bind to membrane components and (or) produce pores

Several categories of antifungal compounds have the capacity to locally induce "pore" formation in biological membranes either through their ability to bind to membrane components (sterols, in particular) or by other means. These molecules are generally amphipathic in nature i.e., they possess both lipophilic and hydrophilic functions that are adept at interacting with or integrating into biological membranes.

Thus, these compounds reduce the membrane's ability to maintain its barrier effect leading to the loss of permeability and the release of intracellular components that are characteristic of their antifungal effect.

Among antifungals in this category, polyenes (polyunsaturated organic compounds that contain one or more sequences of alternating double and single carbon–carbon bonds) are probably the most well known. Polyenes are widely used in medicine to treat mycoses. Although they have not yet found useful applications in plant disease control, their mode of action is classic of pore-forming antifungals. In particular, polyene antifungals associate with ergosterol to produce an aggregate that forms a transmembrane channel (pore) (Vanden Bossche et al. 1994; White et al. 1998). Intermolecular hydrogen bonding interactions among hydroxyl, carboxyl, and amino groups stabilize the channel in its open form, which destroys activity and allows the cytoplasmic contents to leak out. In lieu of polyenes, plants possess compounds in their natural defense arsenal that have equivalent or similar modes of action on fungal membranes: saponins and antimicrobial peptides.

Saponins are part of constitutive plant defense mechanisms in a host of species. The most studied have been avenacin A-1 from oat (*Avena sativa* L.) against *Gaeumannomyces graminis* (Sacc.) Arx & Oliv. var. *tritici* Walker (Crombie et al. 1996) and α-tomatine against a host of tomato (*Solanum lycopersicum* L.) pathogens (Roddick 1974; Steele and Drysdale 1998). They are triterpenoid, steroid, or steroidal glycoalkaloids bearing one or more sugar chains (Osbourne 1996). Their mode of action towards fungi is similar to that of polyenes in that they involve the formation of complexes with membrane sterols. This results in pore formation and loss of membrane integrity. Saponins are considered constitutive plant antifungals. They have not garnered great attention in terms of disease control because they are not easily elicited (artificially augmented) by man-made disease control measures. Moreover, specific fungal pathogens also have the ability to enzymatically degrade plant saponins. However, these factors may provide the basis of a novel strategy through interfering with the pathogen's saponin-degradation enzyme, thus leading to retrieval of effective antifungal activity by these compounds (Osbourne 1996).

Another class of pore-forming antifungals is antimicrobial peptides (AMPs). AMPs are an extremely complex class of antimicrobial compounds, the borders of which remain somewhat vague. Of particular interest, small AMPs, ranging from approximately 12 to 50 amino acid residues, have been identified in a wide range of organisms (animals (including humans), plants, fungi, and bacteria; Bryskier 2005) and have shown broad-spectrum antimicrobial properties (Gram positive and Gram negative bacteria, fungi, and viruses). Among naturally occurring small AMPs, cationic antimicrobial peptides (CAPs) are the most reported in the literature. CAPs are amphipathic molecules that are positively charged because of the presence of excess basic residues, mainly lysine and arginine. The two most common CAP groups are (i) helical linear AMPs (such as magainins and cecropins) and (ii) cystine-rich cationic peptides with one or more disulfide bonds (plant defensins, in particular). Other groups of CAPs containing amino acids other than lysine and arginine do exist as well as synthetic peptides presenting equivalent activities. Moreover, with the advent of synthetic combinatorial libraries, the identification of novel short AMPs (six amino acids) is increasing in the literature (Gonzalez et al. 2002; Reed et al. 1997). Although CAPs have been reported to possess a variety of intracellular activities (Brogden 2005), CAPs are mostly pore-forming molecules that affect the inner membranes of microorganisms (Hancock and Chapple 1999; Lee et al. 2006; Zasloff 2002). The specificity of this mode of action is based on intrinsic microbial membrane features. More precisely, sensitivity to CAPs would be dictated by lipid composition of biological membranes and, more precisely, hydrophobic and electrostatic interactions of CAPs with membrane lipids (phospholipids in particular).

AMPs have been studied and successfully employed in medicine for a number of years (Bryskier 2005; Hancock and Chapple 1999; Lee et al. 2006; Zasloff 2002). However, these peptides have not been nearly as present in a phytopathological context. Some testing on transgenic plants with increased resistance through foreign AMP expression as well as isolated reports on plant defensins have been published. These studies were based on recombinant or natural (elicited) production of AMPs in plants. Reports on the use of AMPs as direct antimicrobial compounds are even scarcer. Naturally occurring and synthetic AMPs have been tested in vitro against tree pathogens (Jacobi et al. 2000; Rioux et al. 2000), although their application in large-scale forestry is deemed more useful in a transgenic tree context. Reed et al. (1997) and Gonzalez et al. (2002) have shown the in vitro effect of synthetic peptides on *Fusarium* spp., *Rhizoctonia solani* Kühn, *Ceratocystis fagacearum* (Bretz) Hunt, and *Pythium ultimum* Trow. Cavallarin et al. (1998), Alan and Earle (2002), Kamysz et al. (2005), and Ferre et al. (2006) have also described CAP derivatives with variable effects on fungal plant pathogens.

Compounds affecting the general membrane lipid domain

Several categories of antifungal compounds, in contrast to the previous group, affect the bulk lipid domain in fungal membranes rather than producing a localized effect. These molecules include antifungal fatty acids and soaps, as well as hydroxy fatty acids and other fatty acid derivatives. These antifungal fatty acids and derivatives are mainly from man-made origins (such as antifungal oils and soaps; Pasini et al. 1997) but have also been reported as part of the inhibitory effect of some plant pathogen antagonists (Avis and Bélanger 2002; Urquhart and Punja 2002) and as plant defense compounds (Hou and Forman 2000; Kato et al. 1985, 1986; Masui et al. 1989).

Antifungal fatty acids and their derivatives are generally of a certain length (normally between 16 and 19 carbon atoms) and are either unsaturated, possess methyl or longer branching or both (Avis et al. 2000). These characteristics are essential in disrupting the general membrane domain. Firstly, fatty acids of the described length easily integrate into biological membranes of fungi (Avis and Bélanger 2001). Secondly, *cis*-unsaturated fatty acids have one or more fixed kinks. This enables the fatty acid to occupy a greater cross section in the membrane than the straight-chained saturated or *trans*-fatty acids. By the same token, methyl or other functional groups placed at a certain dis-

tance from the unsaturation project outward from the fatty acid, thus occupying a larger space in the membrane (Avis and Bélanger 2001). These characteristics disrupt and (or) displace neighboring phospholipid acyl chains leading to an increased fluidity and disorder that is responsible for the antifungal activity.

Antifungal unsaturated and methyl branched fatty acids have been linked to the inhibitory effect of *Pseudozyma flocculosa* (Traquair et al.) Boekhout & Traquair, a biocontrol agent registered for use against powdery mildew diseases in greenhouse crops and flowers (Avis et al. 2000; Avis and Bélanger 2001). A fatty acid ester from *Tilletiopsis pallescens* Gokhale, another antagonist of powdery mildew fungi, was shown to be toxic to *Cladosporium cucumerinum* Ellis & Arth. and *Podosphaera xanthii* (Castagne) Braun & Shishkoff, two cucumber (*Cucumis sativa* L) pathogens (Urquhart and Punja 2002). Hydroxy fatty acids from enzymatic or chemical synthesis or from plants have shown activity in vitro and in vivo against *Erysiphe graminis* DC., *Puccinia recondita* Roberge, *Phytophthora infestans* (Mont.) De Bary, *Botrytis cinerea* Pers.:Fr. (Hou and Forman 2000), *Magnaporthe grisea* (Kato et al. 1986), and *Ceratocystis fimbriata* Ellis & Halst. (Masui et al. 1989).

Compounds that modify permeability through damage to membrane components

A variety of compounds and environmental factors may modify permeability by damaging membrane components. Indeed, ultraviolet light, heavy metals, and salts (among other compounds or factors) have been shown to damage membrane components leading to antifungal activity (Horst et al. 1992).

Recently, inorganic salts have shown antimicrobial activities against fungal pathogens of roses (*Rosa* spp.; Horst et al. 1992), cucurbits (Ziv and Zitter 1992), and potatoes (*Solanum tuberosum* L.; Hervieux et al. 2002; Mecteau et al. 2002) that included a loss of membrane integrity in affected microorganisms (Avis et al. 2007). These salts are particularly effective in the treatment of foodstuff and plant products against postharvest fungal pathogens because direct contact between the salt and the pathogen is usually necessary for effective control. In the particular case of aluminum chloride and sodium metabisulfite, sensitivity to these salts was shown to be linked, at least in part, to elevated levels of lipid peroxidation (Avis et al. 2007). Peroxidation of membrane lipids is a complex process involving unsaturated fatty acids and, in particular, polyunsaturated fatty acid containing one or more methylene groups positioned between *cis* double bonds. These methylene groups are highly reactive to oxidizing agents and can form peroxyl radicals that can set off a free radical chain reaction (propagation phase) to other methylene groups and generate new radical species and peroxidation by-products (Halliwell and Chirico 1993; Marnett 1999), thus damaging membrane acyl chains and affecting membrane integrity. This would explain the high sensitivity of fungi containing highly unsaturated fatty acids (Avis et al. 2007) and would provide measurable biochemical determinants (intrinsic fatty acid unsaturation) that could be useful in predicting the sensitivity of other plant pathogens.

Implications of compounds that target fungal membranes in plant disease control

Antifungals that target specific or general membrane properties have proven or potential efficacy in controlling fungal plant pathogens when usage is based on the knowledge of their mode of action and specific membrane characteristics of the pathogens of interest. However, as with all disease-control methods, precautions must be taken to avoid some of the pitfalls of inappropriate use of an antifungal agent. In broad terms, antifungal compounds fall into two categories in terms of control efficacy: (i) compounds of high (nearly 100%) efficacy with a short longevity and (ii) compounds of lower efficacy with a longer life span. The former category is representative of compounds with specific effects on membrane constituents, whereas the latter is more typical of compounds with generalized effects on membrane integrity. This section will discuss the intricacies associated with some of these compounds and propose strategies to ensure a more reliable efficacy of these membrane-targeting molecules.

First of all, it is important to recognize that compounds with specific effects on membrane constituents, SBI in particular, are some of the most efficient control methods of fungal pathogens. However, the single site of action of SBI has led to the development of fungal strains that are resistant to these fungicides. This resistance is acquired through mutation of the target site of action. This generally renders the fungicide relatively useless when a particular resistant strain appears. In the case of SBI use, resistance management practices is now recommended in most disease-control programs, including alternating or combining SBI with other SBI from different classes (see Table 1) or other antifungals with different modes of action.

On the other hand, compounds with generalized effects on membrane integrity do not generally demonstrate the nearly 100% efficacy in controlling fungal plant pathogens. Whereas compounds targeting the synthesis of specific membrane components affect all fungi that contain the target biosynthetic route (such as SBI), which theoretically affect all ergosterol-containing fungi, the efficacy of compounds that target the general membrane domain is much less clear-cut. This is because fungal cells (i) contain varying intrinsic membrane components across fungal species that are biochemical determinants in tolerance or sensitivity to these compounds and (ii) can adaptively modify their membrane composition and (or) organization when confronted with this type of antifungal. Although this may seems like a drawback for those looking for a "quick-fix," broad spectrum antifungal, these compounds do have a distinct advantage over compounds from the former class in that they are less likely to induce resistance in sensitive fungi (Avis and Bélanger 2001; Zasloff 2002).

The general membrane domain target seems to be the reason behind the reported lack of resistance development in sensitive microorganisms (Avis and Bélanger 2001; Yeaman and Yount 2003; Zasloff 2002). Although cells have the ability to adaptively modify their membrane composition and (or) organization, evolutionary limits are placed on redesigning membranes, and drastic changes in membrane composition are a costly solution in most organ-

isms (Chan et al. 2006). Therefore, this mode of action is extremely difficult to overcome for the affected microorganism, and this tends to delay or even eliminate resistance development in sensitive pathogens (Avis et al. 2000; Avis and Bélanger 2002; Yeaman and Yount 2003; Zasloff 2002). In other words, microorganisms that are intrinsically sensitive to compounds with this mode of action tend to remain sensitive.

In the context of research and development or appropriate use of antifungals that target the general membrane domain, fungal sensitivity in the work reported herein would be dictated by intrinsic membrane constituents. Therefore, it may be possible (i) to predict their relative effectiveness on various plant pathogens and (ii) to select appropriate (tolerant) beneficial organisms (mycorrhizal fungi or biocontrol agents) to be included in the culture system based on these features (Avis and Bélanger 2001).

Compounds from both classes have proven or potential efficacies in the ongoing struggle with fungal plant pathogens. Neither type of compound should be excluded because of their drawbacks in terms of either resistance development (for target-specific compounds) or perceived "partial control" (for compounds with generalized effects on membrane integrity) of fungal pathogens. In fact, recent knowledge about antifungal compounds that target membranes, in particular those with generalized effects on fungal membranes, has shed light on new avenues of research for the efficient and sustainable control of plant disease. Most notably, compounds with generalized effects on membranes are potential candidates for use in combination with disease-control measures possessing other modes of action, because the weakening of pathogen membranes is known to enhance the effectiveness of other antimicrobials (Gonzalez et al. 2002). This last point is of great significance in the case of integrated pest management, considering that these compounds could allow for a decrease in dosage of synthetic pesticides while maintaining their efficacy. Therefore, lowering the dosage of synthetic pesticides could allow for a lesser impact of the direct, indirect, and cumulative effects of synthetic pesticides and could also delay the appearance of isolates resistant to these pesticides, thus lengthening their effective life span.

Conclusion

Antifungal compounds that target fungal membrane components are increasingly widespread in the recent scientific literature. Of particular interest, some of these compounds have demonstrated sought-after characteristics, such as reduced fungal strain resistance and novel modes of action. In particular, compounds with generalized effects on fungal membrane integrity seem to have a bright future as part of an integrated pest management strategy for effective and sustainable plant disease control.

In the ongoing struggle with fungal plant pathogens, there has been increasing pressure on scientists and industry to provide antifungals with (i) high efficacy and (ii) increased longevity. Regrettably, current antifungal compounds seem to fit into only one of the two categories. However, the integrated use of compounds with generalized effects on fungal membranes in combination with compounds with other modes of action have the potential to increase the overall efficacy of disease control while lengthening the life span of synthetic fungicides or other fungicidal compounds that are prone to resistance development. Ongoing research on compounds with deleterious effects on the biological membranes of fungal plant pathogens could well release the untapped potential of these antifungals in plant disease control.

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