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MINI-REVIEW

Cationic surfactants as antifungal agents

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Abstract

Fungi—in being responsible for causing diseases in animals and humans as well as environmental contaminations in health and storage facilities—represent a serious concern to health security. Surfactants are a group of chemical compounds used in a broad spectrum of applications. The recently considered potential employment of cationic surfactants as antifungal or fungistatic agents has become a prominent issue in the development of antifungal strategies, especially if such surface-active agents can be synthesized in an eco-friendly manner. In this review, we describe the antifungal effect and the reported mechanisms of action of several types of cationic surfactants and also include a discussion of the contribution of these surfactants to the inhibition of yeast-based-biofilm formation. Furthermore, the putative mechanism of arginine-based tensioactive compounds as antifungal agents and their applications are also analyzed.

Keywords Cationic surfactants · Antifungal activity · Human pathogens · Antifungal mechanism

Introduction

Despite the high incidence of the increasingly diverse array of fungal pathogens in our daily lives and the proportionally enhanced risks of opportunistic fungal infections, the prevention and treatment options are rather limited (Hanson 2008). Fungi are mainly associated with surfaces' contamination and spoilage of pharmaceutical, cosmetic, and food products (Sandle et al. 2014). Contaminated environmental surfaces provide an important potential source for transmission of not only many health care-associated fungal pathogens, but also those found in recreational public facilities, such as swimming pools and showers. Spores—being able to persist on the environment for long periods of time—can be identified as the main structures responsible for the conquest of new habitats and substrates (Mallo et al. 2017). In this context, environmental disinfection of surfaces, equipment, and devices can be identified as a crucial intervention in the prevention and control of transmission of potentially infectious microorganisms.

Environmental cleaning can reduce contamination on surfaces. However, less than 50% of hospital room surfaces are adequately cleaned and disinfected when chemical germicides are used (Weber and Rutala 2013). Biocides used in pharmaceutical industries and health facilities for the disinfection of medical devices and surfaces of cleanrooms must have a wide spectrum of activity. They must also effectively kill the common types of cleanroom environmental isolates and pathogens, including *Staphylococcus*, *Micrococcus*, *Bacillus*, *Penicillium*, *Cladosporium*, and *Aspergillus* (Sandle et al. 2014). However, among the different microorganisms isolated from cleanrooms, fungi have received less attention than bacteria and the eradication of fungal contaminants in our immediate environment has been found to be an arduous task, and

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many times these practices have been rather a response to an outbreak than a stand-alone activity (Dancer 2009).

Among the ca. five million species of fungi estimated to currently exist, approximately 300 have been recorded to cause disease in humans, but only 20–25 of these do so frequently (Perfect 2017). Within these species, those responsible for superficial fungal infections—in which the pathogen is restricted to the stratum corneum, with little or no tissue reaction—belong to five major fungal phyla (Table 1). Cross-transmission occurrences of these pathogens are mainly indirect through desquamated epidermis or hairs and environmental surfaces, or direct through bodily contact (Hay 2017). For treatment, topical agents—formulated as creams, lotions, or gels—are conventionally preferred, since the side effects are fewer than their internally taken counterparts (Bseiso et al. 2015). However, growing strain resistance has decreased the efficacy of many known and commonly used antifungals, such as fluconazole (Obłąk et al. 2013). To overcome this situation, a new trend in management of fungal infections has considered the use of surface-active agents depending upon their safety—such as the commercial detergent cetrimide, which has proven to be efficient against fungal keratitis (Mahmoud 2016).

In this review, we discuss the use of cationic surfactants as agents for the prevention of fungal colonization and for the control of fungal environmental contaminations in surfaces and devices, providing also an insight into the main mechanisms involved in these features. Furthermore, we will illustrate the role of model-membrane systems in the study of the interaction of bioactive compounds with the fungal membrane as the main target. These kinds of data can become a powerful tool for medicinal chemistry and pharmaceutical technology through the design and optimization of the antifungal activity of novel compounds that exert their activity at surface level.

What do we know about surfactants?

The term *surfactant* has its origins in the combination of the words *surf*ace-*act*ive agent, whereas the suffix *-ant* refers to performing a specific action. According to the *Encyclopædia Britannica*, surfactants are compounds that, when added to a liquid, reduce its surface tension. From the historical point of view, surfactant compounds were originally intended for cleaning. At the present time, however, these agents possess a plethora of applications, from being general detergents (as with sodium lauryl ether sulfate) up to acting as specific biocides that are never used as detergents (such as the fungicide dodine).

In general, surfactants are ingredients in many products used in daily life—such as cleaners (soaps and detergents for industrial, institutional, and home use), pharmaceutical formulations, food, agrochemicals, plastics, personal care, and cosmetics, among others. Because of their ability to reduce the surface tension between immiscible systems (liquid/liquid or solid/liquid), surfactants are mainly used as emulsifiers, dispersants, solubilizers, and wetting and foaming agents. These properties are based on their amphiphilic nature: surfactant molecules have two main functional moieties, one polar (i.e., water-miscible), the other nonpolar (i.e., oil-miscible).

Owing to their numerous applications, surfactants are chemicals that experience a great demand worldwide. The global requirement for these compounds was 15.9 million tons in 2014 and is expected to reach 24 million tons by 2022 (Grand View Research 2016). The world market for surfactants was estimated at 30.7 billion dollars in 2015 and at an annual growth of around 5%. Consequently, the market forecast is expected to reach 45.0 billion dollars by 2024 (Acmite Mark 2016). This market boosting is mainly a result of the rising concerns of people regarding health and personal care all over the world (6.3% from 2015 to 2022); other influences include the increasing demand for oil-field chemicals, as well as other technological innovations (Occams Business Research & Consulting 2017).

According to the combined hydrophilic and hydrophobic handles of the molecule, surfactants can be classified as anionic, cationic, zwitterionic (amphoteric), or nonionic (Florence and Atwood 2006). Among all these classes of surfactant, the anionic ones are by far the more widely used, thus holding the largest market share, mainly for their use as household cleaners and certain pharmaceutical formulations. In general, the anionic surfactants are sulfonates: linear alkylbenzene, secondary alkane, alpha-olefin, and methyl ester sulfonate, with the first of those being the most commonly used for detergents and other cleaners for the last 30 years (Hayes 2009; Gong et al. 2016). Zwitterionic, or amphoteric, surfactants may develop a positive or negative net charge depending on the pH. This class has low foaming characteristics and good wetting properties, imparting mildness to personal care formulations especially. The alkyl betaines as well as the alkyl amidopropyl betaines are the most representative among this type of compound (Johansson and Somasundarau 2007). Nonionic surfactants are mainly represented by alcohol ethoxylates; this class is used principally for defoaming and as solubilizing agents in pharmacons (e.g., polysorbates and sorbitan esters among others; Florence and Atwood 2006; Johansson and Somasundarau 2007). Finally, among the four classes of surfactants, the cationic group is expected to be the faster to grow in the world market in the near future, primarily owing to the multifunctional role of these surfactants in cosmetics and pharmaceutical formulations (Occams Business Research & Consulting 2017).

Among the different parameters that can be taken into consideration to classify these compounds, surfactants can be also categorized according to their origin into synthetic surfactants or natural class—also known as biosurfactants—, the latter

Table 1 Examples of fungal species responsible of human superficial infections

Phylum*	Subphylum*	Class*	Order*	Genus*	Species*	Type of mycosis
Basidiobolomycota	*Basidiobolomycotina*	*Basidiobolomycetes*	*Basidiobolales*	*Basidiobolus*	*B. ranarum*	Subcutaneous and gastrointestinal disease
Entomophthoromycota	*Entomophthoromycotina*	*Entomophthoromycetes*	*Entomophthorales*	*Conidiobolus*	*C. coronatus*, *C. incongruus*	Central facial disease
Mucoromycota	*Mucoromycotina*	*Mucoromycetes*	*Mucorales*	*Apophysomyces*, *Mucor*, and *Rhizopus*	*R. oryzae*	Cutaneous mucormycosis
Ascomycota	*Saccharomycotina*	*Saccharomycetes*	*Saccharomycetales*	*Candida*	*C. albicans*, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis*	Superficial candidiasis
	Pezizomycotina	*Dothideomycetes*	*Pleosporales*	*Alternaria*	*A. alternate*	Keratitis, ulcers, cysts, opportunistic human infections, allergic bronchopulmonary mycosis
			Capnodiales	*Hortaea*	*H. werneckii*	Tinea nigra
		Eurotiomycetes	*Chaetothyriales*	*Cladophialophora*	*C. bantiana*	Brain abscesses, keratitis, ulcers, cysts, cerebral phaeohyphomycosis
				Exophiala	*E. dermatitidis*	Subcutaneous phaeohyphomycoses after traumatic implantation, keratitis, pneumonia, otitis
				Fonsecaea	*F. pedrosoi*	Chromoblastomycosis
				Phialophora	*P. verrucosa*	Chromoblastomycosis
				Rhinocladiella	*R. similis*	Mycetoma and chromoblastomycosis
			Eurotiales	*Aspergillus*	*A. fumigatus* and other *Aspergillus* species	Superficial aspergillosis (mainly *A. fumigatus*), otomycosis, keratitis, and onychomycosis
				Penicillium	*P. marneffei*	Keratitis and otomycosis
			Onygenales	*Coccidioides*	*C. immitis*	Valley fever
				Epidermophyton	*E. floccosum*	Tinea
				Hystoplasma	*H. capsulatum*	Histoplasmosis
				Microsporum	*M. canis*, *M. audouinii*, and *M. gypseum*	Tinea
				Paracoccidioides	*P. brasiliensis*	Paracoccidioidomycosis
				Trichophyton	*T. rubrum*, *T. tonsurans*, *T. mentagrophytes*, *T. verrucosum*, and *T. schoenleinii*	Tinea
		Sordariomycetes	*Hypocreales*	*Fusarium*	*F. solani*	Opportunistic skin infections, mycetoma, human fusariosis, keratitis
			Microascales	*Pseudallescheria*	*P. boydii*	Mycetoma
			Ophiostomatales	*Sporothrix*	*S. schenckii*	Sporotrichosis
			Sordariales	*Madurella*	*M. mycetomatis*	Black-grain mycetoma
Basidiomycota	*Ustilaginomycotina*	*Malasseziomycetes*	*Malasseziales*	*Malassezia*	*M. furfur*, *M. globosa*, and *M. sympodialis*	Pityriasis versicolor, seborrhoeic dermatitis, and folliculitis
	Agaricomycotina	*Tremellomycetes*	*Trichosporonales*	*Trichosporon*	*T. asahii*, *T. ovoides*, *T. inkin*, and *T. mucoides*	Trichosporosis (white and black piedra), opportunistic pathogen

*Taxonomic levels are defined according to Tedersoo et al. (2018) and MycoBank (2018)

being produced by living organisms, mainly microorganisms (Tripathy et al. 2018). Biosurfactants consist of glycolipids, neutral lipids, and lipopeptides, as well as other molecules of larger molecular mass such as lipoproteins and complexes formed by lipopolysaccharides and proteins in addition to complexes of polysaccharides, lipids, and proteins (Hayes 2009). Synthetic equivalents to biosurfactants can be designed imitating natural amphiphilic structures such as phospholipids, alkyl glucosides, and acyl amino acids. This review will focus on synthetic cationic surfactants, particularly on those based on amino acids, and their use as antifungal agents.

Can cationic surfactants help to control fungal environmental and superficial contaminations?

We need to remark here that the amino acid-based surfactants are not commonly used as detergents, since these compounds exhibit a lower foaming capacity than their anionic counterparts (Johansson and Somasundarau 2007). Nevertheless, this class has many other applications—e.g., a retardation of steel corrosion in strongly acidic media (Aiad et al. 2014a; Shaban et al. 2015a, b; Hegazy et al. 2016) and the removal of heavy metals (chromium and arsenic) that are present in industrial wastes like oxyanion environmental contaminants (Li et al. 2002; Li et al. 2003; Gecol et al. 2004) along with environmental uses such as functioning as flushing additives for clearing Cs^+ and radionuclides from contaminated soils (Mao et al. 2015), assisting in the dewatering of activated sludge (Wang et al. 2014), and enhancing oil recovery (through a tailor-made mixture of cationic and anionic surfactants) by reducing crude oil-water interfacial tension and thus producing a flow of oil, among others (Li et al. 2014; He and Xu 2017).

Notwithstanding, apart from this compatibility with industrial and environmental applications, the most relevant property of cationic surfactants with respect to the enhancement of human well-being is their biocidal ability against a wide range of microorganisms. This feature together with their amphiphilic nature makes them powerful additives as well as active compounds by themselves for use in different pharmaceutical, medical, and cosmetic products, though up to now cationic surfactants have been used traditionally as disinfectants (Florence and Atwood 2006; Johansson and Somasundarau 2007). The most well-known compounds of this kind are the quaternary ammonium salts (QUATs, also known as QACs) and esterquats. QACs were introduced in the late 1930s and are considered as *high-production-volume* chemicals. For example, these kinds of compounds are present in about 36% of disinfectant formulations. Their chemical structure is $R_1R_2N'R_3R_4$, (where the Rs are alkyl groups), and they are used mainly in disinfectants and antiseptic formulations of household, industrial, and institutional cleaners; in human and animal health care preparations; and as in agricultural and industrial facility products. Besides their broad antimicrobial spectrum at low concentrations, QACs have many other advantages, such as no color, low odor, high stability, compatibility with the other ingredients in several formulations, and relatively low toxicity (Tezel and Pavlostathis 2015). Within this context, QACs are biodegradable under aerobic conditions and consequently are present in surface waters and sediments in concentrations below their minimum inhibitory concentration (MIC), a property that could lead to the emergence of resistant bacterial strains, including those of certain pathogenic genera, such as the already documented case of *Staphylococcus aureus* (Tezel and Pavlostathis 2015; Jennings et al. 2015). QACs are also toxic to aquatic organisms including algae, fish, crustaceans, and protozoans plus other microorganisms (Chen et al. 2014; Lavorgna et al. 2016; Di Nica et al. 2017). Moreover, though the QACs are extensively used in personal care formulations, those surfactants can prove to be irritants, occasioning different types of dermatitis as well as other allergic eruptions (Anderson et al. 2016; Isaac and Scheinman 2017). For all these reasons, the design and production of alternative cationic surfactants is a topic of utmost interest.

The search for novel cationic surfactants—from those with eco-friendly characteristics to those with improved physicochemical and biologic properties

Bio-based surfactants are all those composed either partially or totally of biologic products (namely, renewable material of agricultural and/or forestry origin) whose production, usage, and disposal have low impact to both the users and the environment (Hayes 2009). Both the safety and the environmental and health profiles of these kinds of products make them not only more attractive to consumers who are concerned about the urgency of ecological issues, but also imperative to any potential users who need to meet the more restrictive requirements and standards exacted by most of the regulations imposed by many governments worldwide (Jessop et al. 2015). The biosurfactants mentioned earlier fall into this category of compounds.

Certain biosurfactants can be taken as models for the synthesis of novel structures. This application has been especially explored in the example of lipoaminoacids and their analogues, all of which compounds can be found in cell membranes. Owing to their structural simplicity, these molecules are relatively easy to design and to synthesize, even in terms of *green chemistry* criteria. Synthons for the production of these kinds of compounds are proteinogenic and nonproteinogenic amino acids for the polar moiety of the molecule and fatty amines or fatty alcohols for the hydrophobic residues

(Infante et al. 2009). Among the plethora of amino acid-based surfactants that can be found in the literature (Gerova et al. 2008; Pérez et al. 2009; Pang and Chu 2010; Tripathy et al. 2018), the arginine-based surfactants are among those with the most striking properties, mainly given by the guanidinium group present in the side chain of the amino acid, which moiety is positively charged at neutrality but also even at high pH levels. Comprehensive reviews can be found on the physicochemical and biologic features of amino acid- and arginine-based surfactants in particular (Pinazo et al. 2011; Lozano et al. 2011; Chandra and Tyagi 2013; Singh and Tyagi 2014; Bordes and Holmberg 2015; Pinazo et al. 2016; Tripathy et al. 2018). The arginine-based ones are especially promising in view of their antimicrobial properties, extremely low toxicity, low irritation potential, and more facile biodegradability than that of the QACs. In this regard, the ethyl ester of *N*-lauroyl-L-arginine, commercially known as Mirenat®, is an arginine-based surfactant commonly used as an emulsifier and a preservative in different food products (Terjung et al. 2014; Maier et al. 2014; Manrique et al. 2017; Gaikwad et al. 2017). Despite the actual uses as well as other potential applications that these kinds of compounds may have, such as nanocarriers for gene therapy (Rosa et al. 2007; Jiang et al. 2016; Peña et al. 2017) and drug delivery systems (Tavano et al. 2014; Nogueira et al. 2015), their biocidal activity is as yet incompletely studied since their antifungal action was only investigated against certain *Candida* species and other specific human-pathogenic fungal strains (Morán et al. 2001; Castillo 2006; Colomer et al. 2011; Fait et al. 2018).

Antifungal activity of cationic surfactants

Table 2 summarizes the biocidal effects of cationic surfactants on several fungi and oomycota that have been reported up to the present. Most findings on the antifungal activity of cationic surfactants are with respect to the fungi that belong to the *Ascomycota* phylum as well as certain species from the phyla *Basidiomycota* (e.g., dodemorph acetate, guazatine, lauric arginate) and *Mucoromycota* (e.g., guazatine, lauric arginate) along with those from the phylum *Oomycota* (Kingdom *Straminipila*; e.g., dodine).

Within the context of biologic infections, the central relevance of biofilms comes from their relationship to infections associated with devices of hospital use, such as intravenous and urethral catheters; permanent prostheses, dental or other types; and mechanical heart valves (Desai et al. 2014). Not only can these infections arise from the microbial colonization of the surfaces of the devices and their growth in biofilms, but the detachment of cells from those biofilms can also cause even more severe infections and septicaemia (Jabra-Rizk et al. 2004). So far, only echinocandins and liposomal formulations of amphotericin B have displayed a significant activity against fungal biofilms (Tsui et al. 2016). In fact, the adherence of pathogenic microorganisms to surfaces and tissues—the first step in the formation of biofilms—happens to be an excellent target for antifungal therapies, and a study of the antiadhesive and inhibitory properties of biofilm formation exhibited by compounds with antifungal activity is of utmost relevance.

Dusane et al. (2012) demonstrated that rhamnolipids are efficient biologic surfactants for disrupting preformed biofilms by the yeast *Yarrowia lipolytica*, reducing those structures by 46% at concentrations below the MIC, with sodium dodecyl sulfate and cetrimonium bromide (CTAB) being less effective at 38 and 25%, respectively. Regarding cell adhesion, although CTAB was reported to bind to the negatively charged microbial surfaces, alter the surface charge, and prevent the binding of fungal cells to those surfaces, this surfactant was not as effective as rhamnolipids in preventing *Y. lipolytica* adhesion, with the antiadhesive effect of rhamnolipids being significantly higher at an inhibition of adhesion to microtiter plate wells by 50% at the MIC.

Candida albicans—the predominant causal agent of human candidiasis—possesses various virulence attributes including the property of biofilm formation. *Candida* biofilms have been reported to be 30–2000 times more resistant to various antifungal agents than their planktonic counterparts (Hawser and Douglas 1994). Given the increased resistance of such pathogenic microorganisms to the currently used antibiotics and chemotherapeutic agents, natural products such as 4-hydroxycordoin—it was derived from plants—constitute an alternative for the prevention and treatment of such infections (Messier et al. 2011). Farnesol also has been described as acting as a naturally occurring quorum-sensing molecule that inhibits biofilm formation, thus indicating the potential of this natural intermediate in the biosynthesis of cholesterol for further development and use as a novel therapeutic agent (Ramage et al. 2002).

Holtappels et al. (2017) investigated the influence of oleylphosphocholine (OlPC) on three different developmental stages of biofilms on catheters—inhibition of cellular adhesion and/or biofilm development, and disruption of preformed biofilms—of 14 strains and clinical isolates of *C. albicans*. This study demonstrated that, although OlPC had no effect on *C. albicans* adhesion, the biofilm development was significantly reduced at low concentrations, thus evidencing also changes in biofilm architecture, as confirmed by scanning electron microscopy. The thick layer of hyphal cells embedded in the material present in nontreated wild-type cells was replaced by a rudimentary biofilm composed of hyphal cells attached to a substrate, and, in strikingly impressive effectiveness, higher concentrations of OlPC completely abolished biofilm development. The authors also investigated the activity of OlPC on in vivo biofilms of *C. albicans* developed in a rat subcutaneous biofilm model, demonstrating that daily oral

Table 2 Reported effects of cationic surfactants on fungi and oomycota

Surfactant*	Fungal taxa and *Oomycota* tested/susceptibility**	Reference
Cetyltrimethylammonium bromide [CTAB]	Complete inhibition of *A. ochraceus*[a] conidia after 3 days when exposed at 0.5%. *C. krusei*[a] FR 01190 was killed within 15 min of contact when applied to 0.5%. While a few cells of *C. parapsilosis*[a] FR-01760 survived if the contact time was less than 60 min, *C. albicans*[a] FR-00806 had no effect when applied at 0.5%.	Gupta et al. 2002
	A. flavus[a] (MIC of0.01 mg/mL), *F. solani*[a] (MIC of 100 μg/mL).	Mahmoud 2016
	A. flavus[a] (MIC_{90} of 8 μg/mL), *A. fumigatus*[a] (MIC_{90} of 16 μg/mL), *A. niger*[a] (MIC_{90} of 8 μg/mL), *Penicillium*[a] spp. (MIC_{90} of 16 μg/mL), *Fusarium*[a] spp. (MIC_{90} of 8 μg/mL), *Cladosporium*[a] spp. (MIC_{90} of 8 μg/mL), *Curvularia*[a] spp. (MIC_{90} of 8 μg/mL), and *Alternaria*[a] spp. (MIC_{90} of 16 μg/mL)	Sandle et al. 2014
	Baker's yeast, *S. cerevisiae*[a]	Raicu 1998
	Several fungi such as *A. niger*[a], *A. ochraceus*[a], *F. solani*[a], *P. minioluteum*[a], and *T. harzianum*[a] were not able to sporulate in vitro at 0.06%. Except for *A. niger*[a], their growth rate was also reduced, but all these fungi were completely inhibited at 0.07%. The *B. bassiana*[a] growth rate was strongly inhibited when applied to 0.06%.	Posadas et al. 2012
	50% viability of *C. albicans*[a] ATCC 90028 at 0.3 mM.	Vieira and Carmona-Ribeiro 2006
	C. gloeosporioides[a] (IC_{50} of the growth: 73.2 μM), *C. lindemuthianum*[a] (IC_{50} of the growth: 79.1 μM), *F. oxysporum*[a] (IC_{50} of the growth: 80.8 μM), *F. solani*[a] (IC_{50} of the growth: 67.9 μM), *T. rubrum*[a] (IC_{50} of the growth: 51.48 μM; MIC_7: 62.5 μM; MIC_{21}: 125 μM), and *T. mentagrophytes*[a] (IC_{50} of the growth: 37.19 μM; MIC_7: 62.5 μM; MIC_{21}: 62.5 μM).	Fait et al. 2018
Dodemorph acetate [Meltatox]	*S. pannosa*[a] var. rosae (recommended dosage for its control, 200 μg/mL), *Erysiphe*[a] species, and *S. flocculosa*[a] ATCC 74320	Benyagoub and Bélanger 1995
Dodecylguanidinium acetate [dodine]	Although the *B. bassiana*[a] growth rate was strongly inhibited when applied at 0.046% (95%), the surfactant inhibits sporulation of *M. anisopliae*[a].	Posadas et al. 2012
	When applied as the commercial funguicide, Efuzin 500FW at practical field dose (0.8–1 L/ha) caused complete inhibition of germination of conidia of *C. acutatum*[a], a causal agent of anthracnose of sour cherry.	Tóth et al. 2012
	S. graminicola[d], pearl milletdowny mildew	Deepak et al. 2006
	The surfactant selectively blocked the growth of *A. niger*[a], *A. flavus*[a], *C. cladosporioides*[a], *C. clavisporus*[a], *F. roseum*[a], *H. thompsonii*[a], *N. rileyi*[a], and *Sporothrix insectorum*[a] when applied at 50 mg/L.	Luz et al. 2007
N^{α}, N^{x}-bis (N^{α}-lauroylarginine)-a,x-alkylidenediamide [bis(Args)]	*A. niger*[a] (MIC, 0.10 mM for a gemini compound with two symmetrical C16-long chain groups linked by a spacer chain of C2 or C4; 0.19 mM for a gemini compound with two symmetrical C16-long chain groups linked by a spacer chain of C6; 0.24 mM for a gemini compound with two symmetrical C12-long chain groups linked by a spacer chain of C2; 0.16 mM for a gemini compound with two symmetrical C12-long chain groups linked by a spacer chain of C4) and *C. albicans*[a].	Pérez et al. 1996; Tyagi and Tyagi 2014
Sugar-based gemini cationic amphiphiles	*A. niger*[a] (24.5 mm of IZD by a dodecyl derivative of glucose-based surfactant at 5 mg/mL; 11 mm of IZD by an oleate derivative of glucose-based surfactant at 5 mg/mL; 12 mm of IZD by a dodecyl derivative of fructose-based surfactant at 5 mg/mL; 9 mm of IZD by an oleate	Negm and Mohamed 2008

Table 2 (continued)

Surfactant*	Fungal taxa and *Oomycota* tested/susceptibility**	Reference
	derivative of fructose-based surfactant at 5 mg/mL) and *A. flavus*[a] (18 mm of IZD by a dodecyl derivative of glucose-based surfactant at 5 mg/mL; 25 mm of IZD by an octadecyl derivative of glucose-based surfactant at 5 mg/mL; 9 mm of IZD by an oleate derivative of glucose-based surfactant at 5 mg/mL; 12.7 mm of IZD by a dodecyl derivative of fructose-based surfactant at 5 mg/mL; 12 mm of IZD by an oleate derivative of fructose-based surfactant at 5 mg/mL)	
Octamethylenediamine, iminodi(octamethylene)diamine, octamethylenebis(imino-octamethylene)diamine, and carbamonitrile [guazatine]	Several isolates of *P. digitatum*[a] (3.1 ppm producing an inhibition growth rate of 1.8% to 4.9%), *G. citri-aurantii*[a] (isolate INTA 8 growth inhibited by 4.9% by 3.1 ppm and by 12.6% by 75 ppm).	Gerez et al. 2010
	Several *Candida*[a] strains, including fluconazole-resistant clinical isolates of *C. albicans*[a], *C. krusei*[a], *C. glabrata*[a], and *C. tropicalis*[a] (MIC_{50} values ranging between 10 and 80 μM); but *C. parapsilosis*[a] ATCC 34136 resistant up to ≥ 80 μM of commercial mixture and each the purified components	Dreassi et al. 2007
	Susceptible fungi at 700 ppm with an inhibition halo of 30 mm or more: *A. clavatus*[a], *F. oxysporum*[a], *F. moniliforme*[a], *G. candidum*[a], and *P. digitatum*[a]. Resistant fungi at 700 ppm with an inhibition halo of 22 mm or less: *A. niger*[a], *A. flavus*[a], *Rhizopus*[c] sp., and *Mucor*[c] sp	Maldonado et al. 2005
	S. sclerotiorum[a] (growth was inhibited around 85% by 5 μM). *A. kikuchiana*[a] (ID_{50} was 10 ppm for growth).	Yagura et al. 1984; Maiale et al. 2008
	Tilletia[b] ssp., *Helminthosporium*[a], *Fusarium*[a] ssp., *Septoria*[a], *Ustilago*[b], and *P. italicum*[a].	Atanasov et al. 2016
N^{α}-benzoyl-arginine decylamide [Bz-Arg-NHC_{10}]	*C. gloeosporioides*[a] (IC_{50} of the growth: 61.3 μM), *C. lindemuthianum*[a] (IC_{50} of the growth: 44.8 μM), *F. oxysporum*[a] (IC_{50} of the growth: 70.7 μM), *F. solani*[a] (IC_{50} of the growth: 61.6 μM), *T. rubrum*[a] (IC_{50} of the growth: 52.06 μM; MIC_7: 125 μM; MIC_{21}: 125 μM), and *T. mentagrophytes*[a] (IC_{50} of the growth: 58.15 μM; MIC_7: 125 μM; MIC_{21}: 125 μM)	Fait et al. 2018
N^{α}-benzoyl-arginine dodecylamide [Bz-Arg-NHC_{12}]	*C. gloeosporioides*[a] (IC_{50} of the growth: 168.2 μM), *C. lindemuthianum*[a] (IC_{50} of the growth: 80.3 μM), *F. oxysporum*[a], *F. solani*[a] (IC_{50} of the growth: 21.6 μM), *T. rubrum*[a] (IC_{50} of the growth: 32.39 μM; MIC_7: 62.5 μM; MIC_{21}: 125 μM), and *T. mentagrophytes*[a] (IC_{50} of the growth: 57.85 μM; MIC_7: 125 μM; MIC_{21}: 125 μM).	Fait et al. 2018
Lauramide of L-arginine ethyl ester monohydrochloride; ethyl-*N*″-lauroyl-L-arginate HCl [Lauric arginate, LAE, Mirenat®]	*A. niger*[a] ATCC 14604 (MIC of 32 ppm), *A. pullulans*[a] ATCC 9348 (MIC of 16 ppm); *G. virens*[a] ATCC 4645 (MIC of 32 ppm), *C. globosum*[a] ATCC 6205 (MIC of 16 ppm), *P. chrysogenum*[a] ATCC 9480 (MIC of 128 ppm), *P. funiculosum*[a] CECT 2914 (MIC of 16 ppm), *C. albicans*[a] ATCC 10231 (MIC of 16 ppm), *R. rubra*[b] CECT 1158 (MIC of 16 ppm), and *S. cerevisiae*[a] ATCC 9763 (MIC of 32 ppm).	Kanazawa et al. 1995
N^{α}-Lauroyl arginine methylester (LAM)	*C. albicans*[a] ATCC 10231 (MIC of 64 ppm), *A. niger*[a] ATCC 46604 (MIC of 125 ppm)	Singare and Mhatre 2012
N^{α}-Nonanoyl L-Arginine ethyl ester [NAE]	*C. albicans*[a] ATCC 10231 (MIC of 125–250 ppm), *A. niger*[a] ATCC 46604 (MIC of 250/500–1000 ppm)	Singare and Mhatre 2012
N^{α}-Myristoyl-L-Arginine ethyl ester [MAE]	*C. albicans*[a] ATCC 10231 (MIC of 3.9 ppm)	Singare and Mhatre 2012
Myristamidopropyl dimethylamine [MAPD]	*A. fumigatus*[a] ATCC 10894 ~ 3.5 log reduction at 50 μg/mL, *C. albicans*[a] ATCC 10231 ~ 2.5 log reduction at 25 μg/mL (starting cell density 10^7 CFU/mL)	Codling et al. 2003

Table 2 (continued)

Surfactant*	Fungal taxa and *Oomycota* tested/susceptibility**	Reference
3,3′-(2,7-Dioxaoctane) bis(1-decylpyridinium bromide) [Gemini-QAC 3DOBP-4,10]	*S. cerevisiae*[a] NBRC 10217 (CRIC ≥ 0.4 μM; MFC 6.0 μM)	Shirai et al. 2009
N-(3-(butylideneamino)propyl)-*N*,*N*-dimethylalk-y-1-ammonium bromide [C10BT, C12BT, and C16BT]	*C. albicans*[a] 32, 24, and 22 mm/mg of IZD for C10BT, C12BT, and C16BT, respectively; *P. chrysogenum*[a] 23, 19, and 22 mm/mg of IZD for C10BT, C12BT, and C16BT respectively (isolates obtained from the operation devel-opment Center, Egyptian Petroleum Research Institute, Egypt)	Shaban et al. 2014
N,*N*′-bis(1-alkyloxy-1-oxopronan-2-yl)-*N*,*N*,*N*′,*N*′-tetramethylethane-1,3-diammonium dihalide [n = alkyl chain length; TMEAL-n X, *n* = 6, 8, 10, 12, 14, and X = Cl or Br]	*S. cerevisiae*[a] MIC > 1200 μM for TMEAL-6 Br, 800 μM for TMEAL-8 Br, 320 μM for TMEAL-10 Br, 80 μM for TMEAL-12 Br, 500 μM for TMEAL-12 Cl, and 240 μM for TMEAL-14 Br	Obłąk et al. 2015
	C. albicans[a] MIC > 1200 μM for TMEAL-6 Br, 240 μM for TMEAL-8 Br, 160 μM for TMEAL-10 Br, 80 μM for TMEAL-12 Br, 800 μM for TMEAL-12 Cl, and 500 μM for TMEAL-14 Br	
	R. mucilaginosa[b] MIC > 1200 μM for TMEAL-6 Br, 80 μM for TMEAL-8 Br, 40 μM for TMEAL-10 Br, 40 μM for TMEAL-12 Br, 10 μM for TMEAL-12 Cl, and 80 μM for TMEAL-14 Br	
N,*N*′-bis(1-alkylloxy-1-Oxopronan-2-yl) *N*,*N*,*N*′,*N*′-tetramethylpropane-1,2-diammonium dihalide [n = alkyl chain length; TMPAL-n X, *n* = 10, 12 and X = Cl or Br]	*S. cerevisiae*[a] CIM 40 μM for TMPAL-10 Br, 500 μM for TMPAL-12 Br, and 500 μM for TMPAL-12 Cl	Obłąk et al. 2015
	C. albicans[a] CIM 80 μM for TMPAL-10 Br, 500 μM for TMPAL-12 Br, and 800 μM for TMPAL-12 Cl	
	R. mucilaginosa[b] CIM 10 μM for TMPAL-10 Br, 10 μM for TMPAL-12 Br, and 10 μM for TMPAL-12 Cl	
N-(3-(benzylideneamino)propyl)-*N*,*N*-dimethylalk-yl-1-ammonium bromide [n = alkyl chain length; *n* = 10 I, *n* = 12 II, and *n* = 16 III]	*C. albicans*[a] 25, 31, and 23 mm/mg of IZD for I, II, and III, respectively; *P. chrysogenum*[a] 18, 21, and 17 mm/mg of IZD for I, II, and III, respectively [II (C12) > I (C10) > III (C16)] (isolates obtained from the operation development Center, Egyptian Petroleum Research Institute, Egypt)	Aiad et al. 2014b
Oleylphosphocholine (OlPC)	*C. albicans*[a] MIC_{50} from 1to 4 mg/L; MFC from 2 to 4 mg/L (14 strains and clinical isolates obtained from urinary catheters, blood culture, and disseminated candidiasis tested)	Holtappels et al. 2017
Morpholinium chlorides	*C. albicans*[a] ATTC 10231 and *T. menthagrophytes*[a] ATCC 9533 MFC from 10 to 10,000 mg/mL	Brycki et al. 2010

*Abbreviations commonly found in literature are listed between square brackets

**IC_{50}, concentration value that causes 50% inhibition of growth relative to the control cultures; ID_{50} (50% *inhibitory* dose), *inhibitor concentration* that produces 50% inhibition; MIC (minimal inhibition concentration), the lowest concentration that exhibited a 100% reduction in growth when compared with the control cultures; MIC_7, the lowest surfactant concentration able to completely inhibit fungal growth after 7 days of exposure to the surfactant; MIC_{21}, the lowest surfactant concentration able to completely inhibit fungal growth after 21 days of exposure to the surfactant; MIC_{50}, the lowest concentration of an agent resulting in a growth reduction of ≥ 50% compared to the growth of the control; MIC_{90}, an estimate of the concentration that inhibits 90% of turbidity compared with that of the control cultures; CRIC, critical respiratory inhibition concentration; MFC, minimal fungicide concentration; IZD, inhibition zone diameter

[a] Phylum *Ascomycota*

[b] Phylum *Basidiomycota*

[c] Phylum *Mucoromycota*

[d] Phylum *Oomycota* (Kingdom *Straminipila*)

administration resulted in a significant inhibition of *C. albicans* biofilms after 9 days of treatment.

In another study, Obłąk et al. (2015) conducted similar experiments testing adhesion, biofilm development, and disruption of preformed biofilms of *C. albicans* and *Rhodotorula mucilaginosa* induced by the alanine-derived gemini quaternary ammonium bromides TMPAL-10 Br and TMEAL-12 Br. The deposition of gemini QACs on polystyrene plates inhibited the adhesion of *R. mucilaginosa* cells, with, of the two, TMPAL-10 Br exhibiting a stronger antiadhesive effect

that caused a higher proportion of killed cells, as evidenced by fluorescence microscopy and a LIVE/DEAD Viability Kit™. With respect to the disruption of *R. mucilaginosa* and *C. albicans* biofilms on polystyrene microplates, the two gemini QACs tested were efficient, with TMEAL-12 Br manifesting a slightly stronger effect. Finally, both gemini QACs exhibited antiadhesive properties upon investigation of *C. albicans* adhesion to silicone catheters. Only TMEAL-12 Br, however, was able to reduce previously formed biofilms on those surfaces.

Within the same context, several patents have described the use of cationic surfactants in the removal of biofilms in industrial systems and in lines and tubing through penetration and dispersal (Hollis et al. 1995; Labib and Lai 2000; Baldridge and Michalow 2004). In addition to the disinfectant properties of cationic surfactants, those compounds—and particularly the quaternary amines—exhibit a strong interaction with cell wall constituents of the microorganisms present in biofilms and thus can facilitate the solubilization of the bacterial and fungal matter in the biofilm. Furthermore, these surfactants provide a certain minimal foaming action to an aqueous cleaning solution that helps to provide a turbulent flow in the tubing to be cleaned as well as aiding in loosening the biofilm or debris from the tubing surface.

Bullseye: the plasma membrane

In view of the negative net charge of bacterial and fungal cellular surfaces, that many antimicrobial agents are cationic and have a high binding affinity to microbial cells is hardly surprising. In the example of the cationic surfactants, the presence of a strong positive charge together with a hydrophobic region is more than enough of a characteristic to enable an interaction with the cell surface and facilitate an integration into the cytoplasmic membrane (Gilbert and Moore 2005). The source of the cationic charge can be variable, but in many instances, that property can be attributed mainly to the presence of ammonium—i.e., CTAB or guanidinium groups—as in the example of N^{α}-lauroyl-L-arginine and dodine, whose structures are illustrated in Fig. 1.

Guanidine moieties are known to form complexes with phospholipid head groups by bidentate hydrogen-bonded ion pairing. This affinity for phospholipids is thought to be responsible for the interaction of those residues with cell membranes and the resulting cell penetration ability and consequent antimicrobial activity (Palermo and Kuroda 2010).

Different mechanisms have been found to be involved in the antifungal activity of the cationic drugs commonly employed for the treatment of fungal infections. In general, the main targets are cell wall polymers—e.g., glucans, chitin, mannoproteins—, the cell membrane, ergosterol, DNA, the protein synthesis machinery—topoisomerases, nucleases, elongation factors, and *myristoylation*—, and the signal transduction pathways—e.g., protein kinases and protein phosphatases (Sant et al. 2016). Table 3 summarizes the putative mechanisms described in the literature for the cationic surfactants commonly used as antifungal agents.

An elucidation of the role of lipids in pathogenesis and target identification for improved therapeutics was pursued by researchers mainly during the last few years (Sant et al. 2016). A targeting of the fungal cell membrane, the conventional approach, has been extensively explored for the development of antifungal agents. Apart from containing ergosterol, the fungal cell membrane is also rich in glycerophospholipids and sphingolipids, which components play an essential role in cellular functions and signal transduction pathways (Dupont et al. 2012). Whereas glycerophospholipids are composed of glycerol-3-phosphate containing two fatty-acyl chains along with various polar substituents—like choline, serine, and ethanolamine—, sphingolipids have a backbone of *N*-acylated phytosphingosine or ceramide. Phospholipids such as phosphatidic acid, phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine, phosphatidylglycerol, phosphatidylinositol, and cardiolipin along with sphingolipids such as inositol-phosphate ceramide, mannosylinositolphosphate ceramide, and mannosyldiinositolphosphate ceramide are reported as cell membrane constituents in *Saccharomyces cerevisiae* (van der Rest et al. 1995). In studies comparing the phospholipid and sterol composition of the plasma membrane of fluconazole-resistant clinical *Candida albicans* isolates to that of fluconazole-sensitive ones, Löffler et al. (2000) revealed no differences in the phospholipid and sterol composition in most of the strains tested (Löffler et al. 2000), though one resistant

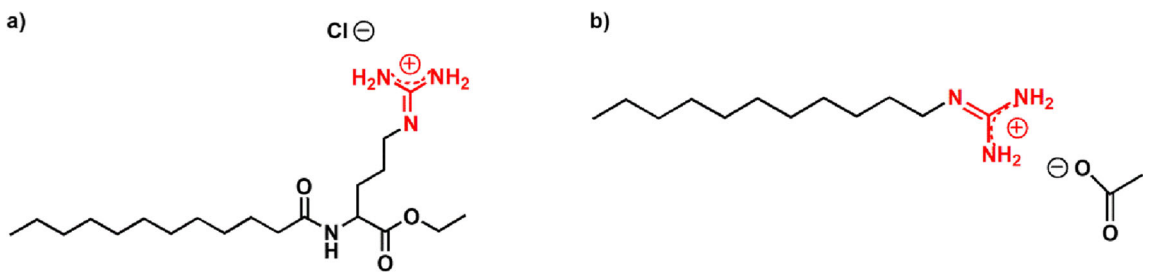

Fig. 1 Chemical structure of **a** N^{α}-lauroyl-L-arginine and **b** dodine. The guanidinium group is indicated in red

strain manifested a decreased amount of ergosterol and had a lower PC/PE ratio than that of the sensitive strains. These authors suggested that those changes in the plasma membrane lipid and sterol composition might be responsible for an altered uptake of drugs and thus for a reduced intracellular accumulation of fluconazole, thereby providing a mechanism for that azole resistance.

Amphiphiles are known to interact with lipid membranes so as to affect their structure. For example, natural amphiphiles can be integrated into lipid bilayers or can completely destroy the bilayer structure to form mixed lipid-surfactant micelles depending on the amphiphiles' critical micelle concentration. In the particular example of CTAB, the critical phenomenon responsible for the antifungal effect of that compound was suggested to be the reversal of the cell surface charge from negative to positive without disrupting the cell membrane, thus enabling the surfactant to penetrate the cell wall (Vieira and Carmona-Ribeiro 2006). In this regard, Shirai et al. (2009) described how another family of cationic surfactants, the gemini QACs, was able to penetrate the cell wall and membrane of *S. cerevisiae*, inhibit respiratory enzymes localized in the mitochondria, and/or destroy organelle membranes. This evidence led to the assumption that the gemini QAC surfactants produced changes in the permeability of the cytoplasmic membrane in order to reach the interior of the cell.

Table 3 Reported mechanisms of action of antifungal cationic surfactants

Surfactant	Putative mechanism of action	References
bis(Args)	Cell membrane with increased permeability	Pérez et al. 1996; Tyagi and Tyagi 2014
Bz-Arg-NHC_n	Permeabilization and direct damage of the plasma membrane Induction of oxidative stress	Fait et al. 2018
CTAB	Membrane solubilization with cell lysis at high concentrations Increase in membrane-surface folding and cell shrinkage, affecting the apparent capacitance of the plasma membrane Reduction of conductivity in cytoplasm and vacuole interior Change of cell-surface charge from negative to positive Protein-function alteration	Raicu 1998; Gupta et al. 2002; Vieira and Carmona-Ribeiro 2006; Posadas et al. 2012; Sandle et al. 2014; Mahmoud 2016; Fait et al. 2018
Dodine	Interference of cell functions (multisite activity) Inhibition of respiration of glucose and acetate and active transport of phosphorus and carbon Sporulation and conidial-germination inhibition	Szkolnik and Gilpatrick 1969; Yoder and Klos 1976; Deepak et al. 2006; Luz et al. 2007; Tóth et al. 2012; Posadas et al. 2012
3DOBP-4,10	Alteration of membrane permeability Inhibition of respiratory function (inhibition of respiratory enzymes and/or destruction of organelle membranes)	Shirai et al. 2009
Guazatine	Inhibition of lipid biosynthesis and oxygen uptake Interference with membrane structure Disturbance of membrane function Membrane destabilization and increased permeability	Yagura et al. 1984; Maldonado et al. 2005; Dreassi et al. 2007; Maiale et al. 2008; Gerez et al. 2010; Atanasov et al. 2016
LAE	Membrane solubilization with cell lysis Interference with membrane structure Loss of membrane potential Cell permeability alteration Leakage of cellular constituents	Kanazawa et al. 1995
Meltatox	Inhibition of sterol biosynthesis (inhibition of $\Delta 8 \rightarrow \Delta 7$ isomerase), causing the accumulation of fecosterol and ergosta-8-en-3ß-ol in *Ustilago maydis* and *Saccharomyces cerevisiae* and fecosterol and ergosterol-8,22,24(27)-trien-3ß-ol in *Botrytis cinerea* and *Penicillium expansum*	Benyagoub and Bélanger 1995
MAPD	Membrane damage	Codling et al. 2003
QACs	Alteration of membrane permeability Leakage of cellular constituents At high concentrations, can solubilize hydrophobic cell membrane components by forming mixed micellar aggregates Disruption and denaturation of structural proteins and enzymes	Hegstad et al. 2010

Model membrane systems for the study of the antifungal mechanism of amphiphilic compounds

A study of the interaction of bioactive compounds with biomembranes—a complex phenomenon from both the chemical and the physicochemical points of view—may provide fundamental information about the mechanism involved, thus expanding our knowledge and offering an opportunity to identify further potential therapeutic targets. Within this context, and in consideration of the role of the plasma membrane, experiments involving different types of model membranes—such as lipid mono- or bilayers or lipid vesicles (liposomes)—are therefore of paramount necessity in guiding the development of new antifungal agents.

Membrane models differ in their complexity (e.g., monolayers, supported bilayers, or vesicles) as well as in their lipidic nature (e.g., saturated or unsaturated lipids, zwitterions, or charged lipids) and their physical state (involving the fluidity or rigidity of the acyl chains). Nevertheless, a simple lipid mixture composed of 75 mol% 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine and 25 mol% 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phospho-l-serine has been found to match the fluidity and charge of the phospholipid composition in the ascomycete (example in point, *C. albicans*) cellular membrane (Stenbæk et al. 2017).

Valuable information about antifungal mechanisms based on membrane interactions can be obtained through membrane models along with other biophysical techniques. González-Jaramillo et al. (2017) have performed a detailed biophysical study on the interaction of the biosurfactant fengycin C with model dipalmitoylphosphatidylcholine (DPPC) membranes (González-Jaramillo et al. 2017). Combining differential scanning calorimetry and fluorescence polarization probe measurements with Fourier transform infrared spectroscopy, those authors demonstrated that fengycin C alters the thermotropic phase transitions of DPPC and is laterally segregated in the fluid bilayer-forming domains, without affecting the hydrophobic interior of the membrane. Fengycin-rich domains, where the surrounding DPPC molecules are highly dehydrated, may well constitute sites of membrane permeabilization leading to a leaky target membrane.

Studies on the plausible mode of action of cationic surfactants support a membranolytic or detergent-like effect similar to that of many membrane-active antimicrobial peptides that should make the development of a complete resistance difficult for the microorganisms (Bahar and Ren 2013).

The example of the Bz-Arg-NHC$_n$ family of arginine-based surfactants

In the particular example of arginine-based surfactants, our own previous work evidenced that, according to the relationship between the chemical structure and the biologic activity of the Bz-Arg-NHC$_n$, the shortness of the alkyl chain was correlated with the strength of the fungistatic activity, whereas, for the bactericidal and/or bacteriostatic capability, the length the alkyl chain correlated with the extensiveness of the antimicrobial potency (Fait et al. 2015; Fait et al. 2018). Considering the differences between bacterial and fungal cells, we suggested that the hydrophobic character of the surfactant molecules might lead to a less efficient internalization, probably because of a strong interaction of those amphiphiles with the fungal lipid membrane. According to Castillo et al. (2006), the difference observed in the behavior of this kind of surfactant towards bacteria and fungi could be explained on the basis of an adequate lipophilic-hydrophilic balance of the molecule, which causes a disruption of plasma membranes or affects intracellular processes, which actions are described in the previous section (Castillo et al. 2006). This hypothesis could explain the higher fungicidal effect of Bz-Arg-NHC$_{10}$ than Bz-Arg-NHC$_{12}$ for almost all the fungal species tested so far.

The analysis of fungal membrane integrity and the qualitative production of reactive oxygen species (Fig. 2) suggested both membrane permeabilization and the induction of oxidative stress to be a part of the antifungal mechanism involved in the interruption of normal conidial development by Bz-Arg-NHC$_n$ (Fait et al. 2018).

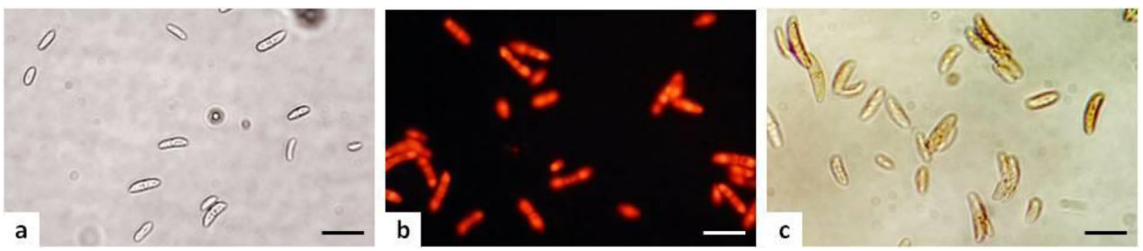

Fig. 2 Antifungal mechanism by of Bz-Arg-NHC$_n$. **a** Control *Colletotrichum* spp. conidia. **b** Membrane permeabilization (evidenced by propidium iodide uptake) induced in conidia of *C. lindemuthianum* by exposure to 400 μM Bz-Arg-NHC$_{12}$. **c** Detection of reactive oxygen species (evidenced by the uptake of the substrate 3,3-diaminobenzidine) produced in the conidia of *C. gloeosporioides* through the exposure to 400 μM Bz-Arg-NHC$_{12}$. Bars: 30 μm (for more details see Fait et al. 2018)

On the basis of the internalization of surfactant molecules as part of the antifungal mechanism and the presence of the arginine moiety in these surfactant species, different models can be proposed to explain their translocation into the cytoplasm through the membrane: (i) direct uptake, which internalization would involve destabilization of the membrane in an energy- and temperature-independent manner; (ii) inverted micelle formation; (iii) pore formation; and/or (iv) electroporation-like permeabilization (Bechara and Sagan 2013). In view of the molecular structure of Bz-Arg-NHC_n, the truncated conical shape of these molecules supports the hypothesis that deals with the formation of transient pores as the main mechanism. In general, facilitation of pore formation by molecules with a positive spontaneous curvature (such as lysophospholipids) is explained by a decrease in the free energy per unit length—i.e., the line tension—that is required to form the edges of a pore whose overall geometric monolayer curvature is positive. In contrast, nonlamellar lipids with a negative intrinsic curvature (such as PE) increase that free energy of pore creation. In a toroid, a positive curvature is found perpendicular to the plane of the membrane, whereas a negative curvature is present in that plane all around the pore. Considering that (i) PE—with an inverted conical shape—may adopt different structures in the membrane, i.e., lamellar or inverted micelles, (ii) strong head group interactions will be established through the formation of H bonds, and that (iii) fungal membranes are rich in PE, a transient pore formation—through which the surfactant molecules can translocate and/or diffuse and reach the cytoplasm—would be the most appropriate mechanistic model for explaining the antifungal effect of these surfactants (Fig. 3). Nevertheless, in order to confirm our hypothesis, further trials with model membrane systems still are needed.

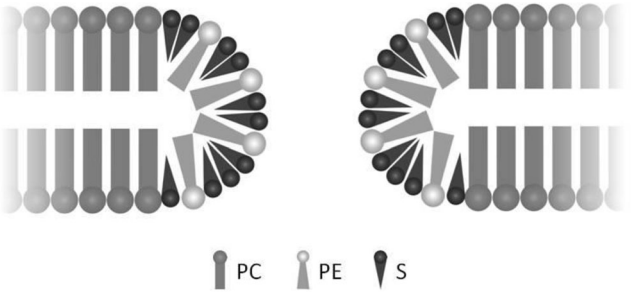

Fig. 3 Transient pore formation as the proposed model for the effect of Bz-Arg-NHC_n surfactants on fungal membranes. On the basis of fungal membrane's composition—rich in phosphatidylethanolamine—and because strong head group interactions could be established through the formation of H bonds between the surfactant head group and the hydrophilic portion of phospholipids, transient pore formation could facilitate the translocation and/or diffusion of surfactant molecules into the cell cytoplasm. PC phosphatidylcholine, PE phosphatidylethanolamine, S Bz-Arg-NHC_n

Uses of cationic surfactants as antifungal agents

Cationic surfactants as antifungal agents can be considered as multisite-active compounds since those amphipaths can exert their antifungal activity through different modes of action. Indeed, such detergents can accordingly be used as fungicides

Table 4 Common uses of cationic surfactants for fungal control

Surfactant	Uses
CTAB	Chemical agent with fungicide or fungistatic activity
	Potential use in treatment of mycotic corneal ulcers
Meltatox	Systemic fungicide used in agriculture
Dodine	Fungicide with preventive action and curative effect especially indicated for the control of scabies in apple and pear. The surfactant also has an eradicating effect when applied 30 to 36 h after the infection was produced. It is used to control scabies in pecan nuts; leaf spot on cherries, olive, redcurrants, celery, and other crops as well as leaf diseases in strawberry and can be used for other fruit plants, ornamental or otherwise. The cationic tenside type dodemorph isomers and dodine as well as the phosphonic acid salts were also well tolerated by pearl millet germlings. Multisite contact activity
Guazatine	The surfactant is widely used in agriculture to control a wide range of seed-borne diseases of cereals. On citrus fruit, it is used as a bulk dip after harvest and in the packing line as a spray. A commercial product, it is a nonsystemic-contact fungicide with potent anti-*Candida* activity, superior to that of the commercial fluconazole, and is a polyamine-oxidase inhibitor in plants with a $K_i \sim 10^{-8}$ M.
Iminoctadine	Protectant. Control of fungal pathogens on citrus, ornamental and fruit trees, lawns and turf. Usually formulated as a seed dressing
LAE	Preservative for the food industry. Commercialized as *Mirenat*™
MAPD	Contact lens multipurpose disinfecting solution, commercial name Opti-Free Express™ (Alcon)

and/or as fungistatic agents. Depending on where in the disease cycle or deterioration process those cationic surfactants act (Balba 2007), they can play a role as (i) protectants (through contact) or preventive fungicides that are effective before colonization, such as in the example of dodine and iminoctadine; (ii) curative agents that are effective against the fungus growing in the host tissue or the fungal product deposited after the occurrence of the infecting spores' germination and therefore have curative properties; and (iii) eradicants or antisporulant fungicides that are capable of stopping sporulation by the organism, as reported for dodine. These compounds can furthermore be used in the field of agriculture to control postharvest diseases as well as in human and veterinary medicine as antifungal agents in topical formulations against opportunistic mycoses in addition to being disinfectants. Table 4 summarizes common uses of cationic surfactants as antifungal agents.

Perspectives

At the present, amino acid-based cationic surfactants are recognized not only as potential antifungal agents, but also as promising enhancers and solubilizers of the already existing antifungal drugs, by that means contributing to a widening of the therapeutic window of those pharmacons. Likewise, the use of these compounds for the pretreatment of surfaces represents a promising alternative to the quaternary ammonium salts as biocidal agents with biomedical applications, focusing on the control of the colonization of those sites by pathogenic microorganisms and the subsequent formation of biofilms. Because of all the advantages cited in this review, the arginine-based cationic surfactants deserve the attention of future research in the field of biochemistry and the biomedical sciences as well as in the realm of agriculture and the pharmaceutical and food industries.

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Compliance with ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

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