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Cationic chitosan derivatives as potential antifungals: A review of structural optimization and applications

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ABSTRACT

The increasing resistance of pathogen fungi poses a global public concern. There are several limitations in current antifungals, including few available fungicides, severe toxicity of some fungicides, and drug resistance. Therefore, there is an urgent need to develop new antifungals with novel targets. Chitosan has been recognized as a potential antifungal substance due to its good biocompatibility, biodegradability, non-toxicity, and availability in abundance, but its applications are hampered by the low charge density results in low solubility at physiological pH. It is believed that enhancing the positive charge density of chitosan may be the most effective approach to improve both its solubility and antifungal activity. Hence, this review mainly focuses on the structural optimization strategy of cationic chitosan and the potential antifungal applications. This review also assesses and comments on the challenges, shortcomings, and prospect of cationic chitosan derivatives as antifungal therapy.

1. Introduction

1.1. Global human health and food security threats from fungal resistance

Although the harmfulness of viruses and bacteria is more noticeable, fungi are invisible killers that should never be ignored. In fact, fungi account for most of the recorded global and regional extinctions of all tracked pathogens, and they continue to threaten threatening humans and crops (Goffeau, 2008; Hahn, 2014). Today, the current global mortality rate of fungal diseases now exceeds that of malaria or breast cancer, which is comparable to that of HIV (Brown et al., 2012; Fisher, Hawkins, Sanglard, & Gurr, 2018). Additionally, phytopathogenic fungi cause crop yield reductions of about 20 % worldwide, and further losses of more than 10 % postharvest (Fisher et al., 2012). To date, fungal infections have apparently been largely ignored compared to other types of pathogenic microorganisms, despite their ubiquitous fungal diseases.

The use of antifungal agents is considered as one of the most effective way to reduce and prevent fungal infections. However, the extensive use of chemical fungicides now has led to the increasing resistance of microorganisms, which poses a global public concern (Baker, 2015; Fisher et al., 2018; Monk & Goffeau, 2008; Revie, Iyer, Robbins, & Cowen, 2018).

Most recently, the Centers for Disease Control and Prevention (CDC) of USA warned of a potentially deadly drug-resistant superbug fungus called *Candida auris,* which considers the fungus a "serious global health threat" (Meis & Chowdhary, 2018; Rhodes & Fisher, 2019; Welsh, Sexton, Forsberg, Vallabhaneni, & Litvintseva, 2019). The emergence of resistant strains of fungi is making traditional antibiotic-based therapies less effective. What's worse is that the lag in the development of new antifungal agents make the treatment of fungi face a state of almost no drug availability. Therefore, the prevention and control of pathogenic fungi is becoming increasingly difficult and challenging (Baker, 2015; Fisher et al., 2018; Roope et al., 2019). To address this problem, it is urgently critical to develop new antifungals with high selectivity and novel mechanisms. Thus, there has been considerable interest in the study of the potential application of antimicrobial polymers for fungal disease control in the clinic and the field. Antimicrobial polymers have emerged as ideal candidates to inhibit the spread of antibiotic-resistant infections because of their broad-spectrum antifungal activity, non-specific mechanisms, and long-term efficacy (Ergene, Yasuhara, & Palermo, 2018; Muñoz-Bonilla & Fernández-García, 2012; Timofeeva &

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Kleshcheva, 2011). Among these antimicrobial polymers, chitosan, as a kind of marine biological polysaccharide with good biocompatibility and non-toxicity, has attracted much attention for antimicrobial applications (Casettari et al., 2012; Chuan, Jin, Fan, Zhou, & Guo, 2019; Pillai, Paul, & Sharma, 2009; Shariatinia, 2019).

1.2. The fungistatic and fungicidal mechanism of chitosan and its relation with the induced resistance

Chitosan, the deacetylated derivative of chitin, is a linear polysaccharide of β-(1, 4)-linked N-acetylglucosamine, which is mainly obtained from the waste products of crab and shrimp shells. It has been proven that chitosan has broad-spectrum antimicrobial activity, can inhibit the growth of a variety of fungi, bacteria and yeasts (Bautista-Baños et al., 2006; Rabea, Badawy, Stevens, Smagghe, & Steurbaut, 2003). There is no doubt that chitosan is a potential antimicrobial substance due to its good biocompatibility, biodegradability, non-toxicity, and availability in abundance. As early as 1979, chitosan was proved to have broad-spectrum activity against various fungi (Allan & Hadwiger, 1979). Generally, chitosan has been reported to be very effective in inhibiting spore germination, germ tube elongation, and radial growth (Bautista-Baños et al., 2006). What is more interesting is the generally recognized view that fungi such as yeasts and moulds are more sensitive to chitosan than Gram-negative and Gram-positive bacteria (Badawy & Rabea, 2011; Roller & Covill, 1999). The antifungal activity of chitosan is mostly considered to be fungistatic, rather than fungicidal. For example, it is reported that the antifungal mechanism for *A. parasiticus* is mainly fungistatic, and it is attributed to the high Mw value of the chitosan sample used (Cota-Arriola et al., 2011). However, this view remains controversial. In contrast, some researchers stated that chitosan has expressed fungicidal activity and can completely inhibit certain fungi including *F. oxysporum*, *R. stolonifer*, *Penicillium digitatum*, and *C. albicans* (Bautista-Baños, Hernández-López, Bosquez-Molina, & Wilson, 2003; Bautista-Baños, Hernández-López, & Bosquez-Molina, 2004). Whether chitosan exhibits fungistatic or fungicidal effects. It is now recognized that the electrostatic interaction of protonated amino groups of chitosan on the cell surface of fungal is the key to endow it the ability to bind, alter or destroy microbial cell surface. The biggest difference between the two mechanisms may be that the fungistatic effect is recoverable and reversible, while the fungicidal effect is destructive and irreversible, which is distinct from the traditional low molecular weight antimicrobials (Galván Márquez et al., 2013; Kong, Chen, Xing, & Park, 2010; Raafat, von Bargen, Haas, & Sahl, 2008; Rabea et al., 2003; Verlee, Mincke, & Stevens, 2017). Chitosan is considered an ideal antifungal candidate due to its non-specific mechanism of pathogen suppression. It primarily targets microbial cell walls / cell membranes and shows a less tendency to trigger the development of drug resistance (Rabea et al., 2003; Verlee et al., 2017; Xing et al., 2018). Developing resistance to chitosan may require fungi to dramatically alter their cell surface structures. In this direction, various chitosan-based antimicrobial strategies have emerged, which can provide promising solutions to this global problem of drug resistance.

However, chitosan is a weak class of polyamine with a pKa of around 6.5, which imparts pH-responsiveness. Chitosan shows antifungal activity only under acidic conditions. The low charge density results in low solubility at physiological pH, aggregation of chitosan and instability of chitosan-based formulations (Mao, Sun, & Kissel, 2010; Szymańska & Winnicka, 2015). In addition, its antifungal activity is far from satisfactory compared with that of traditional fungicides. These factors greatly limit the practical application of chitosan.

Fortunately, it is easy to chemically modify chitosan to improve its physical characteristics such as solubility and antifungal properties because of the presence of attractive reactive sites such as hydroxyl and amino groups in the chitosan backbone. Interestingly, structural modification generally does not change the basic properties of chitosan itself, but does introduce new properties. The molecular structure of chitosan enables it to undergo many reactions, such as cross-linking, oxidation, reduction, complexation, halogenation, phosphorylation, acylation, and so on, resulting in different derivatives (Mourya & Inamdar, 2008; Sahariah & Másson, 2017; Shahid ul & Butola, 2019; Zargar, Asghari, & Dashti, 2015; Zhang et al., 2010). Among these derivatives, cationic chitosan derivatives, including quaternary ammonium salts, have been the most studied. A large number of studies have shown that enhancing the cationic properties of chitosan can not only improve its solubility, but also enhance its activity and extend its applications (Cai et al., 2015; Chethan, Vishalakshi, Sathish, Ananda, & Poojary, 2013; Hoque et al., 2016; Mohamed, Sabaa, El-Ghandour, Abdel-Aziz, & Abdel-Gawad, 2013; Sahariah, Másson, & Meyer, 2018; Wu, Long, Xiao, & Dong, 2016). It is believed that cationic chitosan derivatives with a permanent positive charge generally have better antimicrobial ability than chitosan itself.

In the past two decades, the antimicrobial activities of cationic chitosan derivatives have been extensively studied. In particular, there are a lot of many papers and some reviews on the antibacterial activities of cationic chitosan derivatives (Sahariah & Másson, 2017; Verlee et al., 2017). On the contrary, only a limited number of review articles have been devoted to the antifungal applications of cationic chitosan derivatives. In particular, it is obvious that the strategies and methods of chitosan modification in for antifungals have not been completely concluded and summarized. Therefore, it is necessary to sort out, summarize and provide perspective regarding research progress on the antifungal properties of the chitosan derivatives in recent years.

Hence, the focus of this paper is to describe the structural modification strategy strategies of cationic chitosan and the latest progress in the antifungal activities and the potential medical and agricultural applications. At the same time, we will also summarize and discuss the limitations, challenges and prospects of cationic chitosan derivatives as antifungal candidates.

2. Strategies for increasing positive charge density of chitosan

Chitosan is abundant in nature and it contains three nucleophilic functional groups: C2−NH2, C3−OH and C6 − OH (Fig. S1 in Supplementary data). It can be easily modified on at the amino or C6 C6-hydroxyl groups, while it is difficult to react on at the C3 − OH groups is difficult due to the large steric hindrance. Among these groups, the 2-amino groups are mostly most often chemically modified. This is mainly due to the good chemical reactivity of the 2-amino group, which is easy to carry out allows the grafting reaction to be easily carried out. However, it should be noted that although amino groups of chitosan are more reactive to have nucleophilic reactions than are hydroxyl groups, both active groups can react with electrophilic reagents such as acids, acyl chlorides, and halogenated alkanes, which may modify the amino and hydroxyl groups non-selectively (Sahariah & Másson, 2017; Sashiwa & Aiba, 2004). For example, alkyl halides are often used to prepare chitosan quaternary ammonium salts, but this method usually leads to alkylation of C6 hydroxyl group of chitosan (Rúnarsson, Holappa, Jónsdóttir, Steinsson, & Másson, 2008; Suzuki, Oda, Shinobu, Saimoto, & Shigemasa, 2000). To address this issue and obtain chitosan derivatives with high regioselectivity, different protecting groups can be introduced different protecting groups into C 2 NH_2, C3 −OH and C6 −OH. Phthaloyl groups and Schiff bases are often used to protect the amino group of chitosan (Chen, Tao, Qiu, Ren, & Hu, 2013; Hu et al., 2016; Kurita, Ikeda, Yoshida, Shimojoh, & Harata, 2002; Li, Yang, & Yang, 2015), and triphenylmethyl, trimethylsilyl and tert-butyldimethylsilyl are commonly used to protect the hydroxyl groups of chitosan (Benediktsdóttir et al., 2011; Holappa et al., 2005; Kurita, Sugita, Kodaira, Hirakawa, & Yang, 2005; Rúnarsson, Malainer, Holappa, Sigurdsson, & Másson, 2008).

It is believed that the positively charged amino group of chitosan is the key factor affecting its antifungal activity. In the past 2 decades,

many studies have aimed to improve the activity of chitosan by enhancing the positive charge density. Catatonically charged chitosan can be obtained by various grafting processes, among which, cationic reagents are mostly the most commonly used approaches, which are linked to the chitosan backbone. Therefore, in this review, the most remarkable cationic chitosans, which are classified as quaternary nitrogen atoms, quaternary analogs, polyamines, guanidine, and amino acids/peptides were, are listed and described below (Fig. S2 in Supplementary data).

It should be noted that although chitosan exhibits different activities against fungi and bacteria, the modification strategies are similar to some extent. Hence, before discussing and summarizing the antifungal activity and structure-activity relationship of cationic chitosan derivatives, it should be pointed out that the following modification strategies for improving the cationic properties of chitosan are also common methods to improve the antibacterial activity of chitosan. Some studies have also proven that chitosan derivatives containing cationic groups usually possess both antifungal and bacteriostatic activities (Hassan, 2018; Mohamed & Abd El-Ghany, 2018; Yang, Cai, Hu, Li, & Du, 2012).

2.1. Introducing quaternary ammonium salt groups

Quaternary ammonium compounds (QACs), a class of cationic surfactant broad-spectrum fungicides, are widely used in the paint, water treatment, textile and food industry (Gerba, 2015; Tischer, Pradel, Ohlsen, & Holzgrabe, 2012). For example, dequalinium chloride and benzalkonium chloride, well known in the medical field, are typical quaternary ammonium salt antimicrobial agents. Although QACs have been extensively studied and applied, it should not be ignored that there are also have some problems, such as high toxicity, high volatility and short duration of potency (Sütterlin, Alexy, & Kümmerer, 2008; Zhang et al., 2015). Recently, polymeric quaternary ammonium compounds (PQACs) have attracted increasing attention duo to their higher biosafety and longer-term activity than that of QACs (Jiao et al., 2017; Muñoz-Bonilla & Fernández-García, 2012; Ramos, Forcada, & Hidalgo-Alvarez, 2014). Among them, quaternized chitosan has long been a research hotspot because it not only possesses the typical properties of a quaternary ammonium salt, but also maintains the original good properties of chitosan.

The quaternary ammonium salt of chitosan is mainly prepared by direct quaternization and indirect quaternization. For example, the common method for quaternizing the amino groups of chitosan is by treating chitosan with a halogenated alkane under alkaline conditions (Curti, de Britto, & Campana-Filho, 2003). Another approach is that the amino group on chitosan reacts first with aldehyde, then is reduced by sodium cyanoborohydride or sodium borohydride and finally reacted with haloalkane to obtain the product (Chethan et al., 2013; Liu et al., 2018; Tabriz et al., 2019; Wei et al., 2019). The advantage of this method is that quaternized chitosan products with different alkane substitutions can be obtained (Fig. 1A). The indirect quaternalization approach refers to the introduction of small molecules bearing quaternary ammonium groups including N-(3-chloro-2-hydroxypropyl) trimethyl ammonium chloride (N. A. Mohamed et al., 2013), glycidyltrimethylammonium chloride (Shagdarova, Lunkov, Il'ina, & Varlamov, 2019), (3-bromopropyl) trimethylammonium bromide (de Oliveira Pedro et al., 2013), (5-bromopentyl) trimethy-lammonium bromide (de Oliveira Pedro, Schmitt, & Neumann, 2016), and so on into chitosan molecules (Fig. 1B). Additionally, click chemistry is an ideal method for introducing quaternary ammonium salts into chitosan molecules. `The click reaction has been widely applied in the chemical modification of polysaccharides due to its advantages of high efficiency and selectivity (Meng & Edgar, 2016). For example, Tan et al. reported one kind of cationic chitosan derivative containing 1,2,3-triazole and *N,N,N*-trimethyl groups via an azide-alkyne click reaction, which exhibited enhanced water solubility and antifungal activities (Tan, Zhang et al., 2018).

There are two major advantages of quaternized chitosan over the parent chitosan. After quaternization of chitosan, it becomes a more cationic macromolecule polymer with a permanent positive charge, which correspondingly leads to an increase in solubility and activity (Chethan et al., 2013; Chi, Qin, Zeng, Li, & Wang, 2007; Mi et al., 2018). For example, Wang et al. reported a series of O-quaternary ammonium salt-chitosans (QAS-CS), and found that all QAS-CSs are soluble not only in water, but also in organic solvents such as methanol, ethanol, DMF and DMSO. Moreover, structure-activity relationship studies have shown that alkyl chain length and degree of substitution (DS) are the key factors affecting the antifungal activity of chitosan derivatives. Among them, three derivatives having a medium length alkyl chain and a high degree of substitution showed fungicidal activity, which could inhibit 100 % of the growth of *Aspergillus* and *Canidia albicans* at a concentration of 100 ppm. In contrast, chitosan and BNQAS-CS showed fungistatic activity even at the high concentration of 500 ppm (Wang et al., 2016). The above results indicate that whether chitosan derivatives have fungicidal effects depends on various factors including the DS, derivatization groups, and the tested strains. Sajomsang et al. prepared a kind of water soluble quaternized chitosans and assayed their antifungal activity against *T. rubrum*, *T. mentagrophyte*, and *M. gypseum*. It was indicated that antifungal activity of the chitosan derivatives was affected by the chemical structure, DS and hydrophobic/hydrophilic balance. Moreover, it was proved that introduction certain kinds of quaternary ammonium substituents into chitosan backbone was effective in improving antifungal properties (Sajomsang, Gonil, Saesoo, & Ovatlarnporn, 2012). More reports on the antifungal activity of quaternary ammonium salts of chitosan are shown in Table 1.

2.2. Introducing quaternary ammonium-like salt groups

In addition to the study of chitosan quaternary ammonium salts, analogues of these salts such as pyridinium and quaternary phosphonium salts have shown increasing attention in recent years (Li et al., 2013; Tan, Li et al., 2018; Zhang et al., 2018).

It was proved that N-substituted pyridinium salts possess a broad range of activities such as antiviral, antibacterial, and antifungal activities (Hao, Qin, Zhang, Li, & Zhang, 2019; Sowmiah, Esperança, Rebelo, & Afonso, 2018). In addition, it can be easily dissolved in water. Generally, pyridinium salts are introduced into chitosan by amide bond ester bonds or Schiff bases. To exert synergistic antifungal activity, pyridine rings of chitosan pyridinium salts are usually linked to benzene rings, thiazole rings or other active groups (Fig. 2). In 2010, Li et al. first reported the synthesis and antifungal properties of chitosan pyridinium salts (Li, Guo, & Jiang, 2010). It was found that only the chitosan derivative bearing pyridinium salts exhibited favorable water solubility. If a substituted phenyl is introduced into the pyridine ring, the solubility of the chitosan derivative will significantly decrease due to the introduction of hydrophobic groups. Subsequent antifungal tests showed that the pyridinium salt group could synergize with chitosan and significantly improve its activity (Table 2). For example, the chitosan derivatives exterted significantly enhanced antifungal activities against *C. cucumerinum* and *M. fructicola*, and the inhibitory rate of CHPACS, and BHPACS can reach 100 % at 500 μg/mL, which is much higher than that of chitosan. This indicates that the derivatives have strong fungicidal activity. However, the antifungal activity of the chitosan derivatives was greatly affected by the tested strains. For pathogenic fungus *C. lagenarium* and *F. oxysporum*, the chitosan derivatives exhibited fungistatic effect, which did not show significant improved antifungal properties compared to chitosan.

The structures of quaternary phosphonium salts are similar to those of quaternary ammonium salts. Quaternary phosphonium salts have been investigated and considered as potential next-generation cationic fungicides. First, quaternary phosphonium salts have structures similar to those of quaternary ammonium salts. Moreover, it is reported that

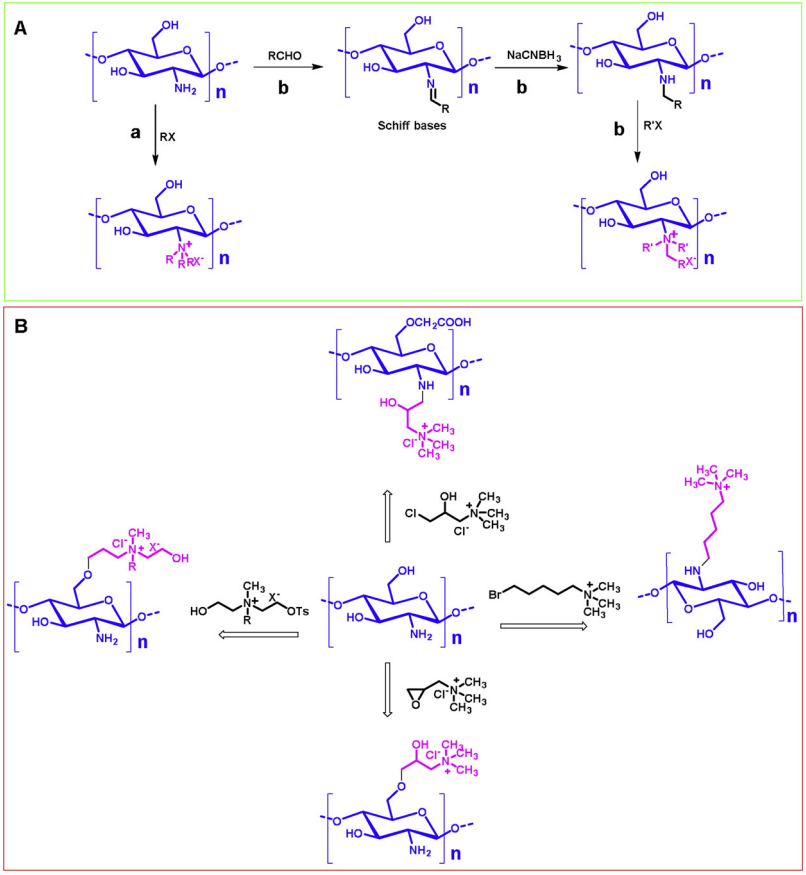

Fig. 1. Common methods to synthesis of quaternized chitosan under direct quaternalization (A) and indirect quaternalization (B).

quaternary phosphonium salts have better antimicrobial activity and biocompatibility than quaternary ammonium salts because the phosphonium groups are more highly positively charged than the ammonium groups (Guo et al., 2014; Li et al., 2017; Wang, Xu, Guo, Peng, & Tang, 2011). Therefore, the introduction of quaternary salt groups to chitosan has recently attracted interest (Qian, Xu, Shen, Li, & Guo, 2013; Sajomsang, Ruktanonchai, Gonil, & Warin, 2010; Zhu et al., 2016). Guo et al. reported the preparation and antibacterial activity of N-triphenyl phosphonium chitosan (Guo et al., 2014). Then Tan et al. succeeded in preparing a class of chitosan derivatives with quaternary phosphonium group (Fig. S3 in Supplementary data). And first described their potential applications as antifungal agents (Tan et al., 2017). These chitosan derivatives were found to have significantly enhanced solubility and antifungal efficiency compared with that of chitosan. The results indicated that quaternary phosphonium groups are very important for enhancing the antifungal activity. For example, in comparison with chitosan, both the obtained chitosan derivatives TCPACSC and TPPACSC exhibited significantly enhanced antifungal activities against three tested crop pathogens. In particular, TPPACSC is more active against *C. lagenarium* with MIC values of 0.05 mg/mL. However, research on chitosan quaternary ammonium salts is relatively rare and requires further study.

2.3. Introducing polyamino groups

It is known that amino groups of chitosan are related to the

Table 1
Antifungal properties of some quaternary ammonium salts of chitosan.

Sample	Molecular weight	Solubility	DS	Antifungal activity[a]	References
CH-Pentyl	20.1 kDa	n.d	64.9	*Aspergillus flavus* (MIC: 500 μg/mL)	de Oliveira Pedro et al. (2013)
C12QAS-CS	4.9 kDa	H_2O (51 mg/ mL)	29.1	*Aspergillus*(100%) *Canidia,albicans*(100%) at 100 μg/mL	Wang et al. (2016)
NCHPDCS	700 kDa	n.d	38.6	*B. cinerea Pers* (86.7 %) at 1000 μg/mL.	Guo et al. (2007))
N-quaternized 6oxychitosan	1600 kDa	H_2O (10 mg/mL)	13.8	*P. hibernalis*(72.8%) at 400 μg/mL	Gao et al. (2018)
HACTFA	200 kDa	n.d	71.39	*C.lagenarium* (96.57%) *B. Cinerea* (86.57%) *P. asparagi* (90.45%) at 1000 μg/mL	Mi et al. (2018)
4CBCTCS	200 kDa	H_2O (1 mg/mL)	51	*F. oxysporum* (88.16%) *P. asparagus* (93%) at 1000 μg/mL	Zhang et al. (2018)

[a] % indicated the Antifungal Index (%), while minimum inhibitory concentration (MIC) is expressed as μg/mL; n.d.—not determined.

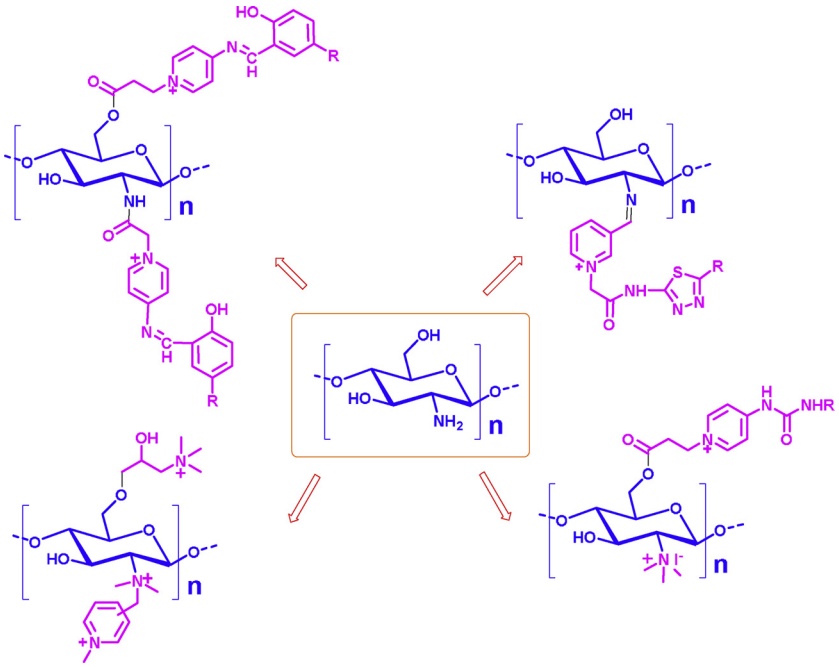

Fig. 2. Some representative chemical structures of chitosan pyridinium salts.

antifungal activity, most likely because of interactions between the positively charged ammonium groups and the negatively charged fungal cell membranes. Therefore, there is no doubt that the number of amino groups in the chitosan molecule is critical for its antifungal activity. However, the reality is that there are only C2 free amino groups in the chitosan structure, which limits the improvement of its antifungal activity. Therefore, increasing the number of amino groups in chitosan may be a promising option to improve its antifungal activity of chitosan. Fortunately, it is possible to increase the number of amino groups in chitosan by converting hydroxyl groups at the C3 and C6 positions to amino groups.

In general, there are mainly two main methods used to prepare chitosan derivatives bearing amino groups: (i) Introduction of amino-containing side chains to the chitosan backbone. For example, Mohamed and El-Ghany prepared a series of modified chitosans with an aminohydrazide group at the C6-position by a four-step reaction. It was demonstrated that the incorporation of aminohydrazide groups is very effective in improving the antifungal activity of chitosan. In particular, the derivative 4/MWCNT1 displayed antifungal activity against *C. neoformans* that was close to that of the positive control drug amphotericin B (Mohamed & Abd El-Ghany, 2018). In 2015, Tiera's group reported synthesis of amphiphilic chitosan derivatives with diethylaminoethyl(DEAE) (Fig. S4 in Supplementary data). The inhibition results show that the attaching DEAE groups alone can significantly increase the solubility of chitosan at a neutral pH. However, this modification does not significantly improve antifungal activity of chitosan, and the hydrophobic Dod groups introduced later can synergize with the DEAE to obviously increase the antifungal activity of CS against *A. flavus* (Fig. S5 in Supplementary data) (Gabriel, Tiera, & Tiera, 2015). More recently, a series of chitosan derivatives of various Mw and fixed contents of DEAE and hydrophobic groups were reported by the same lab to study the mechanism of the antifungal properties against *A. flavus* (Dias et al., 2018). Similarly, the introduction of DEAE groups alone did not significantly improve the antifungal activity of chitosan, but the subsequent hydrophobic modification of chitosan with dodecyl groups improved the antimicrobial activity accordingly. It was found that a lower Mw derivative (DEAE-CH8-Dod) was more effective, completely inhibiting the growth of Aspergillus flavus at 1.0 g/L. However, for chitosan and its hydrophilic derivative DEAE-CH, no inhibitory effect was observed at the same concentration. Obviously, the structural modification has brought fungicidal effect to chitosan. It was inferred that amphiphilic chitosan derivatives can strengthen the interaction with fungal cell walls and thus markedly enhance the antifungal activity of chitosan. In addition, the results of the inhibition mechanism studies show that the amphiphilicity of the chitosan derivatives contributes to the electrostatic targeting of hydrophilic

Table 2
Antifungal properties of some quaternary ammonium salts of chitosan.

Sample	Molecular weight	Solubility	DS(%)	Antifungal activity[a]	References
BHPACS	200 kDa	slightly water soluble	n.d	*M. fructicola* (100%) C.cucumerinum(100 %) at 500 μg/mL	Li et al. (2010)
MTPCTS	70 kDa	n.d	35.7	*P. asparagi* (82.5%) *C. lagenarium* (75.3%) at 1000 μg/mL	Li et al. (2013)
N,O-quaternized chitosan	200 kDa	n.d	92.6	*F. oxysporum* (94.5 %) *fusarium*(99.6 %) *at 1000 μg/mL*	Wei et al. (2018)
Chitosan pyridinium salts	200 kDa	Water soluble	80	*C.lagenarium* (98.44%) *W. fusarium* (79.16%) at 1000 μg/mL	Tan, Li et al. (2018)

[a] % indicated the Antifungal Index (%), while minimum inhibitory concentration (MIC) is expressed as μg/mL; n.d.—not determined.

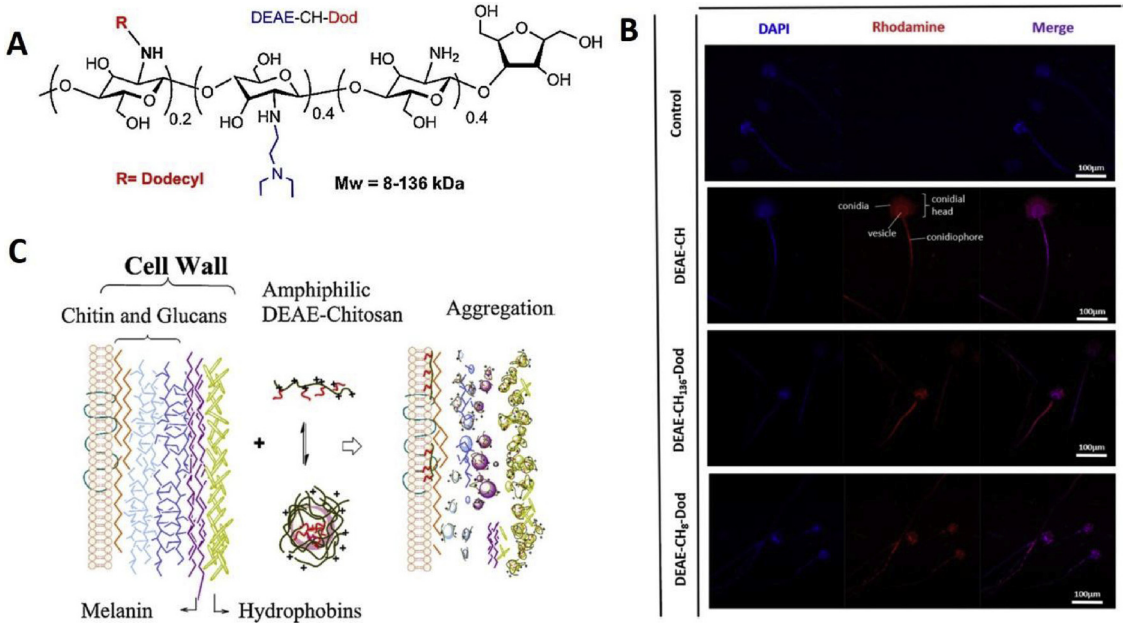

Fig. 3. A) Structure of the amphiphilic chitosan derivatives; B) *A. flavus* under different treatments under a laser confocal scanning microscope (labeled with DAPI as a control); C) Schematic diagram of the amphiphilic DEAE-chitosan adsorption on cell wall and cell membrane and its interaction with their chains and aggregates. Reprinted with permission from Dias et al. (2018).

components and facilitates strong interactions with hydrophobic small molecules present in the cell wall (Fig. 3).

(ii) Reduction reaction of 6-deoxy-6-azido chitosan to obtain 6-deoxy-6-amino chitosan or SN reactions of 6-deoxy chitosan with various amines (Fig. 4). Early in 2004, Satoh et al. first reported the preparation of 6-amino-6-deoxychitosan (Satoh et al., 2006). It was proved that 6-deoxy-6-tosyl chitosan or 6-deoxy-6-halogeno chitosan is a very good starting material for SN reactions (Hu et al., 2016; Tan, Li, Dong, Wei, & Guo, 2016). Thus, they can easily react with various amines to obtain novel C6 substituted amino chitosan. Moreover, 6-deoxy-6-tosyl chitosan and 6-deoxy-6-halogeno chitosan are both important intermediates preparing 6-deoxy-6-azido chitosan, which can yield terminal primary amines via Staudinger reaction and Staudinger ligation (Fox & Edgar, 2012; Koshiji et al., 2016; Luan et al., 2018). However, it is necessary to use triphenylphosphane and remove the resulting triphenylphosphaneoxide, which is not very environmentally friendly. Alternatively, 6-deoxy-6-amino chitosan could also be prepared by reduction of 6-deoxy-6-azido chitosan with $LiAlH_4$ or $NaBH_4$ (Yang et al., 2015).

For 6-amino-6-deoxychitosan, amino groups are present in both the C2 and C6 positions of the sugar unit, so it has a higher positive charge density than that of chitosan under acidic conditions. Previous studies reported by Du's group have shown that 0.1 % 6-amino-chitosan can effectively inhibit the growth of *A. niger*, while the same concentration of chitosan has no antifungal activity. In addition, unlike chitosan, which exhibits antifungal activity only under acidic conditions, 6-amino-chitosan exhibited an inhibitory effect on *A. niger* under neutral conditions (Yang et al., 2012). Recent studies by Luan et al. showed that 6-amino-chitosan(NCS) not only had antifungal activity, of which the inhibitory effect on four tested plant pathogenic fungi was 20 % higher than that of chitosan, but also had good antioxidant properties (Luan et al., 2018).

Considering that the amino group of chitosan is the structural basis of its protonation, our group recently designed and developed another new strategy to increase the number of amino groups recently. That is, on the one hand, we introduced polyamines to increase the protonation potential of chitosan and, at the same time, combined electron-withdrawing groups such as phosphoryl groups to increase the positive charge of on the derivatives. In addition, studies have shown that phosphoryl groups can improve the antimicrobial activity and water

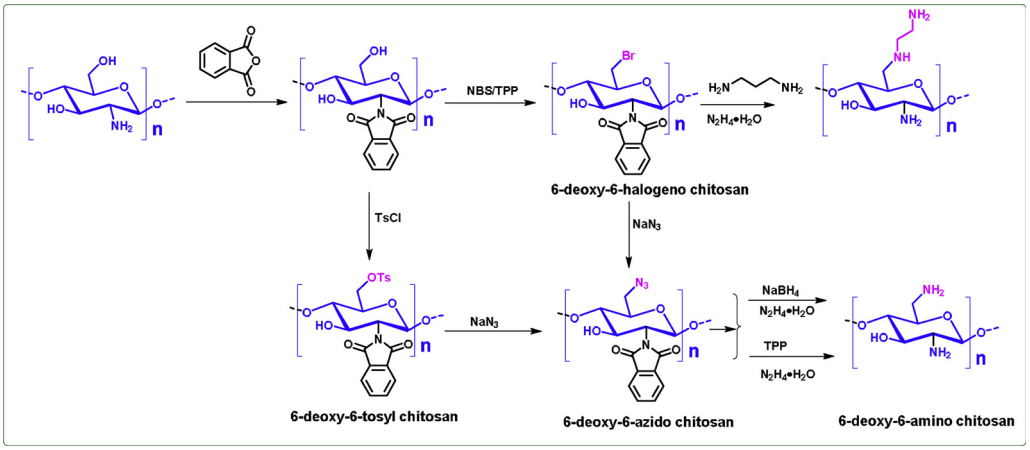

Fig. 4. Common synthetic route of 6-amino-6-deoxychitosan and poly-amino chitosan.

solubility of chitosan (Jayakumar, Reis, & Mano, 2006; Shanmugam, Kathiresan, & Nayak, 2016). Based on the above hypothesis, chitosan derivatives bearing both polyethylamino and diethoxy phorphoryl phosphoryl groups were prepared to study the synergistic effects. Subsequent activity tests showed that the introduction of polyamines and phosphoryl groups not only improved the antimicrobial activity of chitosan, but also allowed its low toxicity to be maintained (Fan et al., 2018).

2.4. Introducing peptides /amino acids

Positively charged antimicrobial peptides (AMPs)/amino acids have shown promising applications as potential antimicrobials due to their high bioactivity and good biocompatibility (Ciumac, Gong, Hu, & Lu, 2019; Pfalzgraff, Brandenburg, & Weindl, 2018; Pinheiro da Silva & Machado, 2012). Interestingly, AMPs with a net positive charge, were thought to be similar to chitosan in term of displaying their selective antimicrobial activity via the disruption of cell membrane integrity. However, in addition to the excellent activity of AMPs against drug-resistant microorganisms, their hemolytic toxicity and cytotoxicity of AMPs to mammals should not be ignored (Maria-Neto, de Almeida, Macedo, & Franco, 2015). To address this problem, there is a growing interest imparting AMPs with the versatility of polysaccharides to reduce the toxicity (Barbosa, Vale, Costa, Martins, & Gomes, 2017; Sahariah, Sørensen et al., 2015). In particular, chitosan is thought to be an ideal material to use for conjugation with AMPs due to its high biocompatibility (Pranantyo, Xu, Kang, & Chan-Park, 2018). Therefore, some recent studies have attempted to obtain new conjugates by coupling chitosan with peptides/amino acids to study whether they have synergistic effects (Kim et al., 2016; Patrulea et al., 2016). For instance, amino acids with hydrophobic, hydrophilic, cationic, anionic characteristics including alanine, isoleucine, lysine and so on have been grafted with chitosan to evaluate the antimicrobial activities (Fig. 5). Chitosan peptide/amino acid conjugates are usually obtained by direct condensation of the carboxyl groups of the amino acids with amino groups of chitosan to form amide bonds. In the process, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) and N-hydroxysuccinimide (NHS) are often used to activate the carboxyl groups of amino acids in the reaction process (Zhou et al., 2019). To avoid side reactions and reduce reaction steric hindrance, some spacer molecules are often used in the coupling process (Table 3) (Denora et al., 2016; Petrin et al., 2019). In some cases, to prevent amino acids from self-polymerization in the presence of EDC, the primary amino groups of amino acids will be protected in advance (Muhsin et al., 2014).

In recent years, a biomimetic strategy inspired by the structure of bacterial peptidoglycan has been very popular in the design and synthesis of chitosan-peptide conjugates (Svendsen, Grant, Rennison, Brimble, & Svenson, 2019; Takahashi, Caputo, Vemparala, & Kuroda, 2017). The newly obtained cationic peptide-polysaccharides with a peptidoglycan-mimetic structure, have been proven to display enhanced biocompatibility while still retaining the antimicrobial efficacy (Fig. S6 in Supplementary data). The coupling methods of AMPs and chitosan usually include copolymerization, condensation and click reaction. Linear chains of linkers are utilized in most cases. For example, Li et al. reported the synthesis of two series of peptidopolysaccharides namely chitosan- graft –polylysine and chitosan-graft-poly(lysine- ran -phenylalanine) via ring-opening polymerization (Li et al., 2012). Patrulea et al. described the preparation of RGDC-functionalized chitosan conjugate by employing a modified sulfo-SIAB method. It was proved that the presence of a diaminohexane (DAH) spacer allows for better control of peptide grafting (Patrulea et al., 2016). In 2015, a kind of anoplin–chitosan C2 amino substituted conjugates through click conjugation were prepared and reported. The authors believed that it was a great importance of coupling peptide on C2 amino of chitosan for maintaining the antimicrobial activity. And they successfully developed a method for performing near-completely selective N-modification of chitosan conjugates via tert-butyldimethylsilyl (TBDMS) protection (Sahariah, Sørensen et al., 2015). Although the main coupling site of

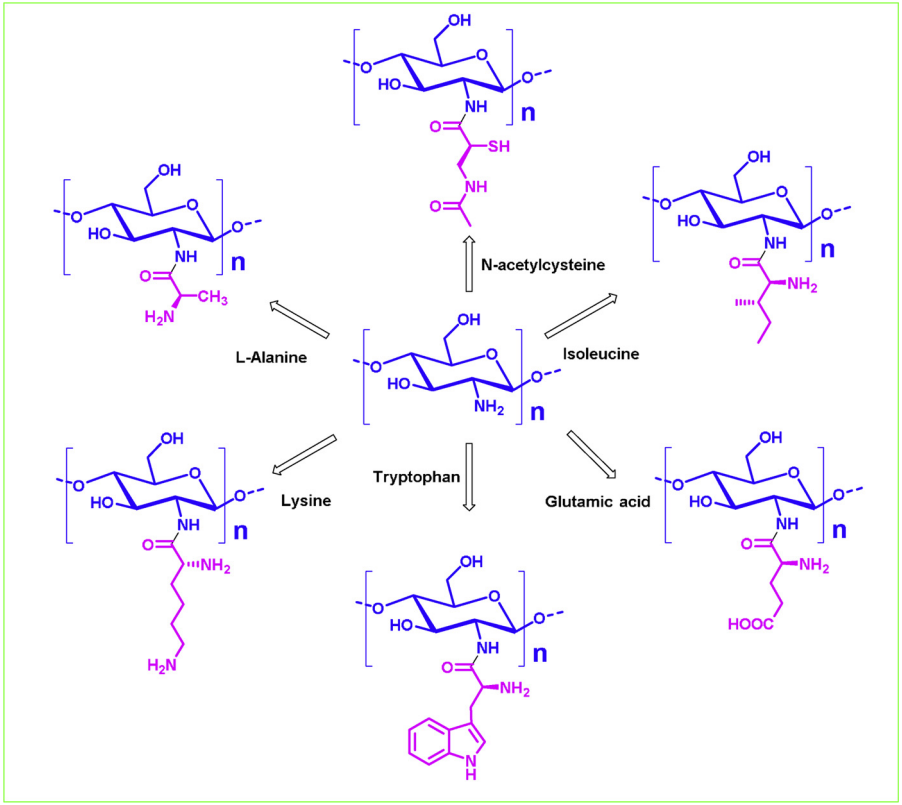

Fig. 5. Some representative chemical structures of chitosan amino acid conjugates.

Table 3
Coupling strategy of commonly used in chitosan peptide/anmino acid conjugates.

Peptide	Linker	Methods of conjugation	Reference
polylysine	/	Copolymerization	Li et al. (2012)
Anoplin peptide	azidoacetyl	Click chemistry	Sahariah, Sørensen et al. (2015)
LED 209	Substituted aminobenzoic acid	EDC/NHS	Zhou et al. (2019)
RGDC peptide	1,6-hexanediamine	Modified sulfo-SIAB	Patrulea et al. (2016)
CysHHC10 peptide	maleimidohexanoic	Thiol-maleimide “click” conjugation	Pranantyo et al. (2018)

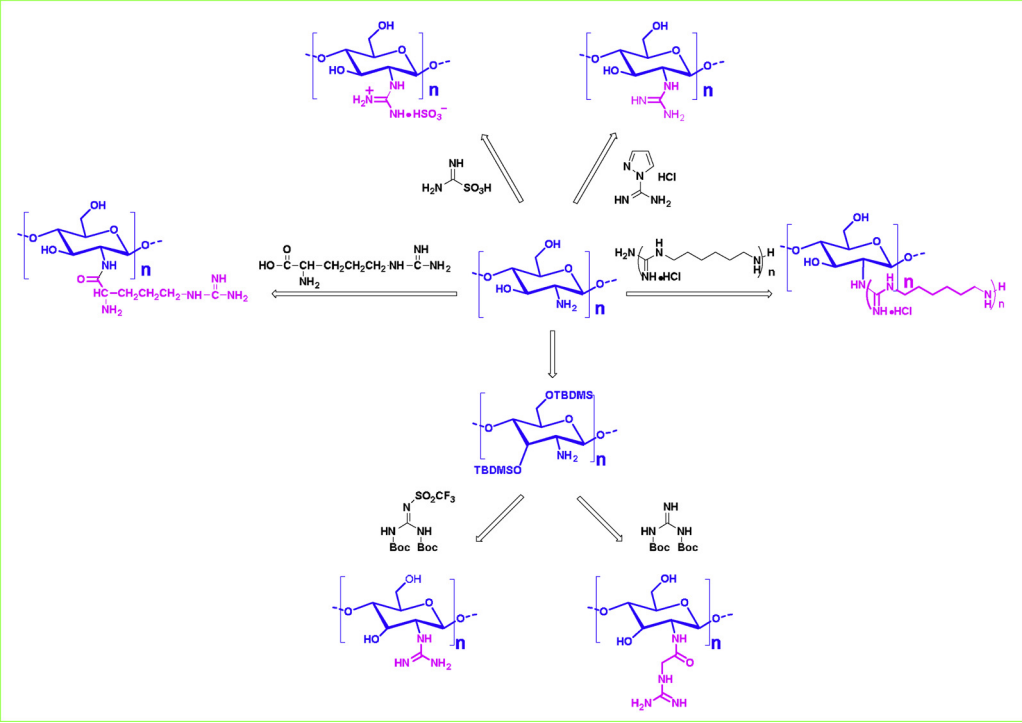

Fig. 6. Typical strategy for the synthesis of guanidinylatzed chitosan.

chitosan peptide is C2 amino, it is still controversial whether 2-position substitution is the most suitable one. Some opinions hold that the amino acid residues in C2 amino-substituted of chitosan differ greatly from those in bacterial peptidoglycans in C3 hydroxyl group. It is argued that the better choice should be that the peptide is linked to the hydroxyl group of chitosan. And in the very recently, Pranantyo and coworkers reported C2 amino and C6 hydroxyl substituted chitosan antimicrobial CysHHC10 peptide conjugates via thiol-maleimide “click” chemistry and compared their activities (Fig. S7 in Supplementary data). It was found that C6 substituted chitosan peptide showed higher activity of than that of C2 substituted. And it was inferred that the existence of C2 free amino group may have a great influence on the activity (Pranantyo et al., 2018).

Before discussing and summarizing the antifungal activity of chitosan peptide (amino acid) conjugates, it should be pointed out that the above strategies are mainly aimed at antibacterial chitosan peptide (amino acid) conjugates. This is because the current research on the antibacterial activity of chitosan peptide conjugates is far more in-depth and sufficient than that on the antifungal activity. However, some studies have also proven that chitosan derivatives containing cationic groups usually possess both antifungal and bacteriostatic activities. Therefore, the above modification strategies are generally applicable to antifungal chitosan peptide conjugates as well. For example, Li et al. reported a new class of cationic peptidopolysaccharides such as chitosan- graft –polylysine(CS-g-Kn) and chitosan-graft-poly(lysine-ranphenylalanine) (CS-g-Kn Fn) by copolymerization of α-amino acids on chitosan (Li et al., 2012). It was found that the antimicrobial activity was influenced by the cationic charge, hydrophobicity and molecular weight. In general, the activity of CS-g-Kn was higher than that of CS-g-KnFn. All tested CSg-Kn samples displayed excellent broad-spectrum activity against common clinical bacteria and fungi and had high selectivity for mammalian red blood cells. This result also clearly demonstrated that the hydrophobicity of chitosan and cationic lysine acid play a synergistic antimicrobial role (Table S1 in Supplementary data). The cationic charge of lysine and the hydrophobicity of the chitosan backbone may help improve the efficiency of the graft copolymer. And it can be also found that the chitosan derivatives of the same type have very different activities (MIC from 5 μg/mL to exceed 2500 μg/mL), which imply that even small changes in structure will have a huge impact on the activity. Among these derivatives, CS-g-K_{16} showed the best antifungal activity. It is speculated that CS-g-K_{16} can exert a fungiicidal effect by penetrating the cell wall and destroying the microbial membrane.

2.5. Introducing guanidine groups

Guanidine, considered one of strongest organic bases, imparts a great cationic character at physiological pH. The unique structural characteristics of guanidine enable it to form non-covalently interactions with some negatively charged components such as phosphates on the cell surface of microbial cell (Amita & Sanjay, 2013). Coupling guanidine side chain with the polymer skeleton can increase its positive charge, which would lead to improved aqueous solubility and potentially enhanced antimicrobial activity (Gorbunova, Lemkina, &

Borisova, 2018). Therefore, guanidine containing polymers are of great interest and have been investigated as potential antimicrobial materials in recent years (Qian, Guan, He, & Xiao, 2008; Qian, Xiao, Zhao, & He, 2011). Among them, guanidinylated chitosan could be expected to serve as an ideal material for antimicrobial application due to their high water solubility, rapid microbicidal properties, and low toxicity (Izawa, Kinai, Ifuku, Morimoto, & Saimoto, 2019; Lahmer, Williams, Townsend, Baker, & Jones, 2012; Salama, Abdel Aziz, & Sabaa, 2018; Su et al., 2016; Sun et al., 2010; Xiao, Wan, Zhao, Liu, & Zhang, 2011).

The synthesis of guanidinylated chitosan generally includes direct and indirect guanidinylation methods (Fig. 6). For direct guanidinylation, the preparation usually proceeds by participation of guanidinylating reagents including chlorcyan, aminoiminomethane sulfonic acid, cyanamide, 1-amidinopyrazole hydrochloride, and so on. For example, Hu et.al firstly reported guanidized chitosan by the reaction of aminoiminomethane sulfonic acid (AIMSOA) with chitosan (Hu et al., 2007). However, it was concluded that the degree of substitution (DS) of chitosan is not very high (in the range of 0.25–0.30) based on the results of elemental analysis, even if the dosage of AIMSOA was increased, the DS does not increase significantly. This result may because in the reaction process of reaction, as the pH value of the system decreases, it is not conducive to the guanidinylation reaction. Guanidine functionalized chitosan can also be synthesized by the reaction of chitosan with cyanamide in aqueous phase (Salama, Saad, & Sabaa, 2017, 2018; Zhai et al., 2011). However, due to the hydrolysis of cyanamide in water, the excessive amount of cyanamide is required, which makes workup difficult and the DS of the desired chitosan derivatives prepared by this method is also not very high. There was a great challenge to prepare guanidine-based chitosan with full substitution by conventional methods. In view of this, some researchers tried to adopt protective group strategy to achieve good control of the reactions and finally successfully prepared completely guanidinylatzed CS (Sahariah, Óskarsson, Hjálmarsdóttir, & Másson, 2015). Although this method greatly improves the DS of chitosan, but it also leads to the increase of reaction steps and the complexity of synthesis because the reaction involves protection and deprotection steps. For indirect guanidinylation, the general method is to couple the reagent containing guanidine group including arginine, *para*-biguanidinyl benzonic acid, 1-(3-(dimethylamino)propyl)guanidine, and so on to the amino group of chitosan. In particular, chitosan arginine conjugates have attracted considerable attention because of the guanidine group of arginine side chains which is similar to the characteristic structure of many antimicrobial peptides (AMPs) (Lahmer et al., 2012; Su et al., 2016; Xiao et al., 2011).

At present, the antimicrobial activity of guanidinylatede chitosan has been widely reported, but the reality is that the current studies are still primarily focused on the effect of inhibiting bacteria. There are very few reports about on the antifungal activity of guanidinylated chitosan, which is similar to the chitosan peptide conjugate discussed above. So far, to the best of our knowledge, only one study reported by Salama et al. (2017). It was found that the inhibitory effect of the chitosan derivatives for all tested fungi was significantly improved in comparison with that of plain chitosan. Among these chitosan derivatives, ChG displayed the best antifungal properties against all tested fungi with MIC values range from 0.49 to 3.9 μg/mL, even comparable to that of positive control amphotericin B drug against *S.recemosum*. However, the author did not clarify whether the derivatives exerted fungicidal or fungistatic effects. As is known to us, the most commonly used method for judging fungicidal or fungistatic effects is the MFC (minimal fungicidal concentrations)/MIC ratio method (Borman et al., 2017; Meletiadis et al., 2007). It is generally considered fungicidal when the value ≤ 4 and fungistatic when the value > 4. Therefore, it is necessary to determine MFC in subsequent studies in order to clarify the antifungal mechanism.

2.6. Physical/ionic strategies

In general, the chemical modification stratiges of chitosan described in the previous section requires multi-step chemical reaction and use of organic solvents that might affect the physical properties of antimicrobial materials and ultimately their biological functions. More importantly, the single-component chitosan derivative cannot meet the antimicrobial needs in some special environments. For example, most of the above-mentioned chitosan derivatives play antifungal effect in a solution state, which limits their applications in in preventing water treatment systems, antimicrobial surfaces, dental and medical devices associated infections. It has been confirmed that the formation of pathogenic fungal biofilm is one of the key factors of fungal resistance (Lynch & Robertson, 2008). Fungal biofilm-associated has recently become a serious clinical problem, which poses a fatal threat to immunocompromised patients (Chandra & Mukherjee, 2015; Desai, Mitchell, & Andes, 2014; Gupta, Daigle, & Carviel, 2016; Suleman, Archer, Cochrane, & Percival, 2014). Fungi like *Candida albicans* can produce biofilms during colonization and infection (Chandra et al., 2001; Gulati & Nobile, 2016; Nobile & Johnson, 2015). Biofilm mediates adhesion to host tissues and medical devices, and protects fungi from attacks by the host immune system and antifungals.

Therefore, in addition to the conventional chemical modification, physical / ionic strategies can also be used to enhance the antimicrobial effect by changing the surface morphology and properties of the chitosan based antifungals. For example, chitosan can form a strong complex with heavy metals such as gold, silver, copper or metal oxides due to the free amino and hydroxyl groups present in its backbone. Therefore, the most common strategy for enhancing the antimicrobial properties of chitosan is to use it in combination with heavy metal metals (oxides) and their nanoparticles (Bui, Park, & Lee, 2017; Il'ina, Shagdarova, Lun'kov, Kulikov, & Varlamov, 2017; Moussa, Tayel, Alsohim, & Abdallah, 2013). Additionally, regarding to the design of antimicrobial surfants, a polyelectrolyte multilayer membrane (PEM) made by layer-by-layer (LbL) technology can serve as a multifunctional platform. There are some studies in LbL entrapment of AMPs and other active ingredients within chitosan polyelectrolytes on textiles and microspheres for oral drugs (Gomes, Mano, Queiroz, & Gouveia, 2015; Guzmán, Mateos-Maroto, Ruano, Ortega, & Rubio, 2017; Huang, Zhang, Cheng, & Xiao, 2019; Jung, Li, Yeh, Ren, & Sun, 2019). To design antimicrobial surfaces and interfaces, there are three main strategies to achieve this goal: anti-adhesion, contact killing, and biocide leaching strategies (Adlhart et al., 2018; Kaur & Liu, 2016; Swartjes et al., 2015). In the first method, the goal is to reduce the ability of bacteria / fungi to adhere at an early stage. This method usually relies on the use of superhydrophobic surfaces. The second method is a contact killing strategy, which attempts to immobilize active molecules (such as quaternary ammonium or antimicrobial peptides). And it will become active when contacted. For example, Jiang et al. developed a new fungal repellent strategy based on Candida favors hydrophobic surfaces (Jiang, Yeh, Wen, & Sun, 2015). And they found that surface of the PMMA discs modified by TMC/SA multilayers reduced the adhesion of fungal cells and effectively prevented the formation of biofilm. This discovery provides a new option for the development of drug-free biofilm-resistant healthcare materials. Although contact active surfaces have the advantage of long-term effect, they may not completely kill the pathogens unless direct contact, especially to the planktonic state of pathogens, and show a fungistatic effect. In the last (and oldest) principle, antibiotics, silver as well as other antifungal agents loaded into the bioactive coating, can release the active molecules and kill planktonic pathogens. The fungicidal effect is fast and efficient. For instance, Regiel-Futyra et al. described the preparation of chitosan–ascorbic acid–silver nanocomposites (Regiel-Futyra et al., 2017). It was found that the nanocomposites exhibited a great bactericidal and fungicidal potential against the tested pathogens as well as inhibition of biofilm formation. Moreover, chitosan–silver nanocomposites showed reduced

cytotoxicity on mammalian, which may be promising antimicrobials candidates However, limitations include short duration of sustained release, potential toxicity and drug resistance. In order to achieve better antifungal effects, the latter two functional principles are sometimes combined to achieve a synergistic effect, such as by embedding a fungicidal substances in a surface with a contact active function.

As mentioned avove, among these antimicrobial strategies, controlled release may be a good strategy to inhibit biofilm formation, while the contact kill strategy has its limitations because it requires direct contact with pathogenic fungi. In the case of biofilm formation, the application of chitosan alone may not be the best choice. It might me a better option to combine chitosan with other active ingredients to exert the best effect.

3. Applications

Although chitosan has proven antifungal properties, it can only dissolve in dilute acid and display antimicrobial activity only under acidic conditions. However, in fact, microorganisms usually live in neutral pH, and many enzymatic biochemical reactions related to life activities are often carried out in aqueous phase. This greatly limits the application of chitosan. On the contrary, many cationic chitosan derivatives obtained by structural modification of chitosan often shows good solubility in a wide pH range as well as satisfactory antifungal activity. In addition, the physical / ionic strategy further enhances the antifungal effect of chitosan and endow it new functions. All these performance changes greatly expand its applications and some representative examples are summarized in Table 4. Considering that there are already some excellent review articles published recently about the applications of chitosan and its derivatives, this article will mainly focuses on several specific application areas including wound dressing, health facility disinfection, antimicrobial textiles, and food packaging materials.

3.1. Wound dressings

Chitosan is known for its hemostatic and antimicrobial properties, which are especially effective for wound management (Dai, Tanaka, Huang, & Hamblin, 2011; Khan & Mujahid, 2019). As a hemostatic agent, chitosan helps to naturally coagulate and stop nerve endings, thereby reducing pain. Chitosan is a positively charged polymeric amine and can attract negatively charged ions as well as pathogens in blood and exudate. Due to the similar chemical structure of chitosan and cellulose, the two are often mixed at the polymer and fiber levels. This hybrid allows manufacturers to design products with the required performance at a lower cost. Chitosan-based hemostatic agent is probably one of the most successful commercial product of chitosan currently developed, and there are several chitosan-based wound dressings on the market for clinical use, including the FDA-approved and commercially available Combat Gauze, Celox Rapid, ChitoGauze, and ChitoFlex.

Recently, it was reported that zinc oxide nanoparticles were incorporated in the chitosan hydrogel to further increase their antimicrobial activity. Addition of zinc oxide improved its flexibility, antimicrobial activity and tensile strength (Sudheesh Kumar et al., 2012). In addition, many current researches have further improved the manufacturing method of the chitosan bandage dressing to enhance its existing hemostatic potential and antimicrobial activity (Bagher et al., 2020; Hamedi, Moradi, Hudson, & Tonelli, 2018). When integrating some antioxidants or coupling to chitosan, the mechanical properties, drug delivery and wound healing properties of the chitosan bandage are improved. By loading active ingredients, it opens up new options for the treatment of chronic wounds in diabetic foot (Moura et al., 2014).

Table 4
Potential applications of cationic chitosan derivatives.

Potential applications	Antimicrobial target	Derivatives type	details	References
Wound dressing materials	*Aspergillus fumigates, Geotricum candidum*	N-quaternizedchitosan/poly(vinyl alcohol) hydrogels	The antifungal activity of NQC/PVA hydrogels is higher than NQC itself, of which the values are compared to Amphotericin B	Mohamed et al. (2015)
Antimicrobial patches and food packaging.	*Aspergillus brasiliensis* and *Aspergillus fumigatus*	chitosan films graft with poly(acryloyloxy) ethyltrimethylammonium chloride	Displayed higher activity against the tested fungi than the origin chitosan.	Hassan (2018)
Clinical practice, pharmaceutical and food industries	*F. oxysporum, A. alternata* and *C. herbarum*	N-[(2-hydroxy-3-trimethylammonium) propyl] chloride chitosan derivatives	Solububle at neutral pH;100 % inhibition of the growth of tested phytopathogenic fungi hyphae at 500 mg/ml	Shagdarova et al. (2019)
Drinking water treatment	*Aspergillus niger, Fusarium solani*	Quaternized N-trimethyl chitosan/polyethersulfone membranes	The functionalized membranes exhibited 72 % inhibitory effect on *Aspergillus niger*	Tabriz et al. (2019)
Biofungicides	*Aspergillus flavus*	chitosan Propyl and Penty trimethylammonium bromides	The antifungal activity is 3–6 times higher than that of commercial chitosan	de Oliveira Pedro et al. (2013)
Antimicrobial agents in topical and other infections	*C. albicans, C. tropicalis, C. dubliniensis, Cryptococcus spp.*	N-(2-hydroxypropyl)-3-trimethylammonium chitosan chlorides	Good inhibitory activity against the tested human pathogenic fungi; Very low in vitro toxicity	Hoque et al. (2016)

3.2. Health facility disinfection

Generally, cationic chitosan derivatives not only has good water solubility and antifungal activity, but also maintains the advantages of good biocompatibility and biodegradability of chitosan. Moreover, it can also be processed by copolymerization, crosslinking, blending, forming complex with metal ions, and so on, so as to obtain materials, such as membranes, gels, coating, scaffolds, for different uses (Hassan, 2018; Mohamed & Abd El-Ghany, 2018; Mohamed, Elella, & Sabaa, 2015; Pranantyo et al., 2018; Tabriz et al., 2019). Among the diverse applications of cationic chitosan derivatives to inhibit fungi, one of the most noticeable may be its disinfection control in clinics, hospitals and some medical environments. The prevalence of fungal infections is on the rise due to the prevalence of immunodeficiency diseases caused by organ transplantation, immunosuppressive therapy, built-in medical device therapy, radiotherapy and chemotherapy, and AIDS (Aslam, Hernandez, Thornby, Zeluff, & Darouiche, 2010; Badiee & Hashemizadeh, 2014; Georgiadou & Kontoyiannis, 2017; Lanternier et al., 2013). The occurrence of fungal resistance is the main reason for the poor anti-fungal treatment (Revie et al., 2018). It's a great challenge to develop novel antifungal materials to prevent fungal biofilm formation. A common approach to address this problem is to design surfaces that release biocides, such as metal ions (such as gold, silver, lead, or arsenic) or chemicals (such as triclosan, chlorhexidine, peroxide, or chlorine). Limitations of these methods include the short lifespan of the biocides released and their potential toxicity. Other strategies have also attempted to address these limitations by developing "contact-killing" antimicrobial surfaces containing covalently attached groups, such as cationic macromolecules containing biguanide, pyridinium or quaternary ammonium salts. For example, Hoque et al. demonstrated that N-(2-hydroxypropyl)-3-trimethylammonium chitosan chlorides (HTCC) display rapid microbicidal kinetics by destroying the cell membrane of resistant fungi. More importantly, the cationic chitosan derivatives exhibit very low toxicity in vitro and in vivo (Hoque et al., 2016). Therefore, these highly selective polymers have potential applications in the dearth of new antibiotics for clinical pipelines. Very recently, Jung et al. report a novel fungal control strategy based on layer-by-layer self-assembly of amphiphilic quaternary chitosan (CS612) / sodium alginate (SA) multilayer coatings on PMMA-based denture biomaterials to Controlling fungal biofilm formation. The multi-layer coating effectively altered surface properties and prevented the formation of fungal biofilms, suggesting that CS612 / SA LBL multilayers had fungal repellency. In addition, the multi-layer coating also has good cell compatibility and stability, which indicates that this new type of coating may have great potentials for controlling fungal biofilm formation in clinically applications (Jung et al., 2019). Although these surfaces can inhibit microorganisms upon contact, their effectiveness is inherently limited to cells in direct contact with the microorganisms. Therefore, in order to exert the synergistic antifungal effect, it will be a better choice to use it in combination with the slow-release sterilization strategy.

3.3. Antimicrobial textiles

Antimicrobial-treated fabrics play a key role in the protection and treatment of appropriate skin injury care. Among many antimicrobial finishing agents, chitosan stands out as a green and environmentally friendly material (Morais, Guedes, & Lopes, 2016; Shahid ul & Butola, 2019). It is rich in resources and has excellent characteristics such as moisture absorption, breathability, high reactivity, biodegradability, adsorption, broad-spectrum antibacterial, and safety and nontoxicity. Chitosan are often used to develop antimicrobial fabrics that are environmentally friendly, broad-spectrum antibacterial, low cost, and comfortable to wear. Chitosan can be well combined with cellulose fibers through hydrogen bonding, so it is often used for antimicrobial finishing of cotton fabrics (Cheng, Ma, Li, Ren, & Huang, 2014; Fu, Shen, Jiang, Huang, & Yan, 2011; Ibrahim, Eid, El-Aziz, Elmaaty, & Ramadan, 2017; Periolatto, Ferrero, & Vineis, 2012). Similar to the antimicrobial surface strategy mentioned above, chitosan's antimicrobial effect in fabrics can also be divided into two types: contact and slow-release active modes. For instance, Xu et al. successfully used carboxymethyl chitosan (CMCTS) and silver nanoparticles to attach to the surface of cotton fabrics by a simple atomization modification process. The CMCTS adhesive is covalently connected to the cotton fabric through esterification, and the Ag nanoparticles are tightly adhered to the fiber surface through coordination bonds with the amine groups of CMCTS. The results showed that the Ag nanoparticle coating on the cotton fabric showed excellent antimicrobial and washing resistance (Xu et al., 2018). Fu et al. (2011) synthesized three different chitosan quaternary ammonium salts and used citric acid as a crosslinking agent to finish cotton fabrics. After finishing, the antimicrobial rates of the finished fabrics against *Staphylococcus aureus* and E. coli were more than 99 % and 96 %, of which O-quaternized-*N*-chitosan Schiff base has the best effect in finishing fabrics.

There has been already a commercial product based on this natural polymer, Eosy®, the composite fiber of chitosan and viscose called Crabyon® is also commercially available and has a long-lasting antimicrobial effect. In addition, textiles are using chitosan-based antimicrobials to prevent infection and / or protective and sportswear is already on the market.

3.4. Food packaging materials

Chitosan and its derivative have broad-spectrum antifungal activity, and can inhibit the germination of sporangia, germination tube and mycelium growth of pathogenic fungi (Badawy, 2010; El Hadrami, Adam, El Hadrami, & Daayf, 2010; Guo et al., 2007; Tan, Ma, Lin, Liu, & Tang, 2013; Tan, Zhang et al., 2018; Xing, Zhu, Peng, & Qin, 2015).

At present, there have been a large number of research reports on chitosan's antimicrobial film for fresh-keeping of fruits and vegetables (Grande-Tovar, Chaves-Lopez, Serio, Rossi, & Paparella, 2018; K, MP, & GR, 2019; Kaewklin, Siripatrawan, Suwanagul, & Lee, 2018; Sangsuwan, Pongsapakworawat, Bangmo, & Sutthasupa, 2016). Studies have found that edible film made of chitosan is an important way to keep fruits, meat, vegetables, and fish fesh. The edible film not only prevents the loss of original nutrients in food, but also plays a role in increasing nutrition and some food additives such as antioxidant. Among them, the application of controlling postharvest diseases and preservation of fruits and vegetables attracts special attention. Infection of pathogenic fungi and deterioration of metabolism are the main causes of fruit decay and deterioration (Singh & Sharma, 2018; Snowdon, 1988). To reduce fungal contamination and related fruit and vegetable decay, antimicrobial coatings and films, especially natural antimicrobial films such as chitosan based films are preferred in the management and control of postharvest diseases (Campos, Gerschenson, & Flores, 2011; González-Estrada, Chalier, Ragazzo-Sánchez, Konuk, & Calderón-Santoyo, 2017; Grande-Tovar et al., 2018; Romanazzi, Nigro, Ippolito, DiVenere, & Salerno, 2002; Sharma, Barman, & Siddiqui, 2016; Valencia-Chamorro, Palou, del Río, & Pérez-Gago, 2011). This is because most of postharvest pathogenic contamination of fresh fruits and vegetables occurs mainly on their surface (Heaton & Jones, 2008), so the application of antimicrobial film is safer and more effective than the application of traditional small molecule fungicides. Therefore, it is a promising preservative for fruits and vegetables (Figure 19) (Dutta, Tripathi, Mehrotra, & Dutta, 2009; Gianfranco Romanazzi, Feliziani, & Sivakumar, 2018). However, when the chitosan derivative films are used alone, there are some shortcomings, such as poor mechanical properties of the film and short retention time of the coating (Cazón & Vázquez, 2019; Oh & Hwang, 2013). If they are mixed with other preservatives by using composite film, nanoparticles, microcapsules and other technologies, they may play a synergistic role, thus expanding their application scope (Saraji, Tarami, & Mehrafza,

2019).

3.5. Other applications

In addition to the applications mentioned above, chitosan has many other potential applications. For example, the incorporating of chitosan into the polymer blend ultimately improved its strength, wettability, resistivity, and antimicrobial activity (Abraham, Soloman, & Rejini, 2016; Lewandowska, 2015; Sionkowska, 2011). Chitosan containing polymer composites can be used as coatings, paints, hydrogels, which have several ranges of applications in the industry (Dutta, 2019). Additionally, chitosan and its derivatives can also be used as drinking water treatment agents and have been approved by the EPA (approval number:SU834295). As a potential biocontrol pesticide, chitosan and its cationic derivative also can be made into seed soaking agents, root application agents, spray agents, film spreading agents, etc (Kumaraswamy et al., 2018). Moreover, they can be used as soil amendment to control soil-borne diseases, as seed dressing agents to control seed-borne diseases, fruit and vegetable preservation to control postharvest diseases (Badawy & Rabea, 2016; Betchem, Johnson, & Wang, 2019; Fan et al., 2018; Kumaraswamy et al., 2019; Zhang, Li, & Liu, 2011). Currently, chitosan and its derivatives have been registered as bio-pesticides in the United States, China and other countries.

4. Challenges and shortcomings

As mentioned in the above review, the feasibility of improving the solubility and antifungal activity of chitosan by increasing its positive charge density has been widely investigated. Overall, these studies indicate that cationic chitosan derivatives have great application prospects for disinfection, postharvest disease control and preservation of fruits and vegetables, etc. However, it should be noted that, although good progress on antimicrobial chitosan derivatives has been made over the past two decades, there are also a series of challenges and shortcomings such as uncontrollable derivative quality, unclear structure-activity relationship, and potential toxicity to mammals. Most importantly, the practical application of cationic chitosan derivatives is progressing slowly. Most of the antifungal activity reported only regards the in vitro activity. There are few reports on clinical or field in vivo tests.

4.1. How to ensure reproducible product quality?

Unlike traditional small molecular weight therapeutics which have a well-defined chemical structure, chitosan derivatives exhibit some heterogeneity as with other polymers. Chitosan derivatives vary with respect to their molecular weights, degrees of substitution, substitution sites, and resulting structural complexity, making the controllable, reproducible, and scalable preparation of chitosan derivatives challenging (Alves & Mano, 2008; Hosseinnejad & Jafari, 2016; Khan et al., 2017; Riaz Rajoka, Zhao, Mehwish, Wu, & Mahmood, 2019; Sahariah & Másson, 2017; Verlee et al., 2017; Zargar et al., 2015). From the perspective of practical application in the future, the synthesis of derivatives should be environmentally friendly, cost-effective, and easy to manufacture at an industrial scale. However, the reality is that structures of the cationic chitosan derivatives usually vary from batches to sources. Moreover, due to the lack of reasonable molecular design in the design and synthesis process, the synthetic derivatives also have problems such as structural heterogeneity, poor chemical selectivity and poor reproducibility (Bellich, D'Agostino, Semeraro, Gamini, & Cesàro, 2016; Carvalho, Queda, Santos, & Marques, 2016; Pillai et al., 2009; Sajomsang, Tantayanon, Tangpasuthadol, & Daly, 2008). Therefore, it is difficult to fabricate a chitosan derivative with reproducible structure and appropriate properties. In addition, the structural complexity of chitosan derivatives poses great challenges to the characterization of their physicochemical properties. Determining how to establish a uniform, accurate and repeatable detection method is another problem that needs to be solved.

4.2. How to accurately determine the structure-activity relationship?

Although it is generally believed that chitosan derivatives have a broad spectrum of antifungal activity, their activities are affected by multiple factors including molecular weight, degree of substitution, hydrophobicity, type of fungus, pH, etc. There have been some excellent reviews on the antimicrobial structure-activity relationships (SARs) of chitosan derivatives (Sahariah & Másson, 2017; Verlee et al., 2017), however, so far there appears to be no precise, universal criterion to predict how the structural parameters determine the properties of chitosan derivatives. In fact, study of the SAR of chitosan derivatives is far from the level of SAR research of small molecule drugs due to the complexity of the structure of chitosan derivatives, as well as lack of special antimicrobial methods and models. It is hard to compare and analyze the antifungal results of the chitosan derivatives obtained by different researchers and draw clear conclusions. There are often large differences in activity in different studies. Some studies even have diametrically opposite results, which makes it difficult to accurately evaluate the structure-activity relationship of chitosan. For example, the degree of substitution(DS) is a key factor affecting the antifungal activity of chitosan. The antimicrobial activity of cationic chitosan derivatives generally improves with increasing DS. However, at the same time, the activity may also be affected by other factors such as hydrophobicity, substitution sites or spacer (Anitha et al., 2009; Badawy & Rabea, 2014; Chethan et al., 2013; Gabriel et al., 2015; Jung, Kim, Choi, Lee, & Kim, 1999; Li, Tan, Zhang, Gu, & Guo, 2015; Sarwar, Katas, Samsudin, & Zin, 2015). Furthermore, for macromolecules such as chitosan, it is a challenge to ensure that each step in the reaction goes to completion under heterogeneous or multistep reaction conditions. Therefore, the subsequent DS calculation and QSAR analysis are also complicated. All of these limitations undoubtedly hinder further development and applications of the chitosan derivatives. To address this problem, it may be a good choice to achieve precise synthesis of specific DS through protection and deprotection strategies. More recently, research has made good progress in this area (Sahariah, Óskarsson et al., 2015).

4.3. How to balance activity and toxicity?

Chitosan is considered to be nontoxic, biocompatible and biodegradable. Research on cationic chitosan derivatives has therefore focused more on the activity, ignoring its potential toxicity. While striving to enhance the antimicrobial properties of chitosan, a low toxicity of chitosan derivatives should be ensured to promote their development into practical applications. Charge density is considered to be a key factor affecting the antimicrobial activity, selectivity and mammalian toxicity of chitosan to pathogens and mammalian cells (Kean & Thanou, 2010; Wang et al., 2016). In general, the antimicrobial activity increases as the positive charge increases. However, cations in chitosan derivatives may also affect the toxicity. In fact, some studies have shown that with increasing positive charge density and concentration, the activity and toxicity of chitosan derivatives increase accordingly (Min et al., 2018; Sahariah et al., 2014). In addition, it has been reported that enhancing the hydrophobicity of the chitosan quaternary ammonium via increasing alkyl chain length also leads to the risk of increased hemolysis and toxicity (Sahariah, Benediktssdóttir et al., 2015). It is speculated that the cationic chitosan derivatives may have a charge threshold, and that once that threshold is exceeded, increasing the positive charge density will not significantly increase the activity, but will increase the toxicity. Therefore, it is important to maintain an appropriate charge density for cationic chitosan derivatives to maximize the antifungal activity and minimize toxicity.

4.4. Lack of in vivo activity data and unclear mechanism of action

Although research on the inhibition of bacteria and fungi by cationic chitosan derivatives has been widely reported and confirmed, it must be acknowledged that the current studies have mainly been in the laboratory stage over the past 2 decades, that most of the research on antimicrobial activity as well as toxicity are in vitro, and that the tested strains are mostly common drug sensitive strains. In contrast, there are very few studies on the in vivo antifungal activity of cationic chitosan derivatives in the literature, and research from clinical trials and field trials is rarely reported. Currently there is very little data on the pharmacodynamics, pharmacokinetics, environmental toxicology, in vivo toxicity of the chitosan derivatives. Furthermore, information on the stability, biocompatibility and biodegradability of cationic chitosan-based antimicrobial membranes, gels, and surfaces is urgently needed. This information is vital for the accurate evaluation of a promising polymer drug in the early stage, and will primarily decide whether it is suitable for further development.

Currently there is no single widely recognized antifungal mode of action for chitosan and its cationic chitosan derivatives (Kong et al., 2010; Lopez-Moya, Suarez-Fernandez, & Lopez-Llorca, 2019). For the antifungal mechanism of chitosan, the prevailing view is that the positively charged amino group of chitosan might bind with the negative charged substance such as phospholipids in the cell wall of the fungi via electrostatic interactions, forming a layer of polymer membrane on the surface of the fungi cell, changing the selective permeability of the cells, thus blocking nutrients from entering the cells, or disrupting the cell membrane, entering the cell, leading to inhibition of DNA/RNA and protein synthesis (Kong et al., 2010; Verlee et al., 2017).

Most of the antifungal mechanism studies to date have only been on the origin chitosan (Martins et al., 2018). Considering that a new functional group is introduced into the chitosan skeleton, sometimes introduction of a plurality of reactive groups brings about the diversity in the structure of the chitosan derivative, and the antifungal properties may be the result of a combination of a plurality of different groups. Therefore, it is difficult to judge whether the antifungal mechanism of chitosan is equally applicable to the chitosan derivatives. Accordingly, more research is needed on the antifungal mechanism of cationic chitosan derivatives.

5. Concluding remarks

The main purpose of this review is to highlight the recent progress in the field of cationic chitosan-based antifungal therapeutic applications. The broad range of properties exhibited by cationic chitosan derivatives indicates that they may have application prospects in many areas of therapeutic need. However, before actual application, these compounds will face a large number of long-term clinical trials or field trials, as well as a very strict regulatory approval process, all of t which requires detailed activity data as a support.

In the future, considering the diversity of the chitosan derivative structure, great efforts are desirable to prepare chitosan derivatives with well-defined structures through biological rational design and appropriate synthetic methods. First, the structural design of chitosan derivatives should be as simple as possible under the premise of ensuring antifungal activity, and the synthesis of the derivatives should be shortened as much as possible to reduce side reactions and the corresponding structural uncertainty of chitosan derivatives. Additionally, since the synthesis of small molecule compounds is more controllable than the modification of macromolecules, it is conceivable to first synthesize small molecule intermediate building blocks and then couple them with chitosan. Moreover, in the process of structural modification of chitosan, functional group protection and deprotection strategies should be adopted to avoid side reactions and improve product substitution. In terms of antifungal activity and toxicity, it is necessary to ensure that the chitosan sample has a clear source, uniform quality and high purity. The strains to be tested should be representative, and in particular, resistant strains should be selected; More importantly, the standard physicochemical characterization methods, strict structure-activity relationship studies, and in-depth in vitro and, in vivo antifungal activity and toxicity tests are extremely important. Most importantly, researchers need to assess whether the chitosan derivatives have the potential to be developed as macromolecular drugs at an early stage and to accurately focus on their possible scope of application, such as oral or topical, and as a drug or as an excipient. All of these approaches require the application of multidisciplinary techniques and methods, and therefore require the collaboration of synthetic chemists, physiologists, clinicians, toxicologists, etc. Nevertheless, more studies are needed for the in-depth evaluation of cationic chitosan derivatives to take full advantage of their therapeutic potential.

In summary, with the advancement of follow-up technologies, more detailed information will be undoubtedly obtained about the antifungal structure-activity relationships and mechanisms of chitosan derivatives with target cells; It is believed that cationic chitosan-based materials will become a powerful and effective tool for antifungal therapy.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.carbpol.2020.116002.

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