Antimicrobial Properties and Application of Polysaccharides and Their Derivatives

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Abstract  With the quick emergence of antibiotic resistance and multi-drug resistant microbes, more and more attention has been paid to the development of new antimicrobial agents that have potential to take the challenge. Polysaccharides, as one of the major classes of biopolymers, were explored for their antimicrobial properties and applications, owing to their easy accessibility, biocompatibility and easy modification. Polysaccharides and their derivatives have variable demonstrations and applications as antimicrobial agents and antimicrobial biomaterials. A variety of polysaccharides, such as chitosan, dextran, hyaluronic acid, cellulose, other plant/animal-derived polysaccharides and their derivatives have been explored for antimicrobial applications. We expect that this review can summarize the important progress of this field and inspire new concepts, which will contribute to the development of novel antimicrobial agents in combating antibiotic resistance and drug-resistant antimicrobial infections.

Keywords Antimicrobial; Drug resistance; Polysaccharides; Polysaccharide derivatives; Chitosan

INTRODUCTION

Microbial infection is a common community and nosocomial acquired disease that has been a global challenge and seriously threatens the health of human life.\textsuperscript{[1]} Although anti-microbial treatment has made great progress in the past century, infectious diseases are still one of the three leading causes of death in the world according to the report of the International Health Organization.\textsuperscript{[2]} In recent years, multdrug resistant microbial infections have been increasingly serious problems, especially with drain of the antibiotic pipeline.\textsuperscript{[3]} As reported, the global death toll caused by drug-resistant bacterial infections will increase from $7 \times 10^5$ in 2015 to $1 \times 10^6$ in 2050, if without effective action and strategy.\textsuperscript{[4]} Therefore, it is in great need to develop novel antimicrobial agents for variable applications. There are many glycoconjugates or glycoconalix that cover the surfaces of mammalian cells. In the process of microbial infection, pathogens usually use glycoconjugates to recognize and bind to host cells.\textsuperscript{[5]} The changes of glycans over time and space reflect strategies that pathogens use the host surface to evade defense.\textsuperscript{[6]} Therefore, polysaccharides are a class of natural polymers worth exploring for the antimicrobial applications.

Polysaccharides have many important physiological functions such as promoting the production of various cytokines (e.g. interferon, interleukin, etc.), stimulating macrophages and lymphocytes, and promoting antibody production to enhance organismal immunity.\textsuperscript{[7]} In addition, polysaccharides also have antiviral, antibacterial and anti-inflammatory functions to some extent, mainly by inhibiting viral and bacterial reproduction.\textsuperscript{[8,9]} The excellent biocompatibility, wealthy resources and low prices of polysaccharides altogether result in the increasing interest in exploring polysaccharides and their derivative as emerging antimicrobial agents.

Various polysaccharides exist in nature, such as chitosan, dextran, hyaluronic acid, cellulose and other plant/animal-derived polysaccharides, which have been explored for antimicrobial applications. In this review, we attempt to provide an overview on the development of polysaccharide-based antimicrobial agents and their applications, and a prospective on the future of this field (Scheme 1).

CHITOSAN

Chitosan, $\beta$-(1→4)-2-amino-2-deoxy-D-glucose, the product of partially or fully deacetylated chitin, is the second most abundant natural polysaccharide after cellulose.\textsuperscript{[10]} Chitin mainly
exists in the shells of crustacea, such as crab and shrimp, cell walls of fungi, algae and plants. Chitosan is the only basic polysaccharide in nature, bearing free amino group. Due to its unique biological characteristics, such as biodegradability, biocompatibility and bacteriostasis, chitosan has been widely used in food, textiles, agriculture, environmental protection, cosmetics, biomedicine and other fields.

**Antimicrobial Mechanism**

In 1979, Allan et al. proposed broad-spectrum antibacterial properties of chitosan. Since then, chitosan has been widely studied and applied in various fields. Chitosan can inhibit the growth of bacteria and chitosan-sensitive fungi. In general, according to the different targets of chitosan on cells, its antibacterial mechanism can be divided into two categories (Fig. 1). Young et al. proposed that chitosan targets bacterial cell membranes. Briefly, under acidic conditions, the amino groups on chitosan are protonated to show positive charges and bind to the surface of negatively charged bacteria. The uniform distribution of charge on the bacterial cell wall is disturbed, which affects the synthesis of the cell wall or even destroys the cell wall. Without cell wall protection, the permeability of cell membrane changes greatly and the cell contents leak out. Another mechanism proposed by Roller suggested that chitosan could penetrate through the porous cell wall of bacterial and enter into the bacteria after chitosan is adsorbed on bacteria. Chitosan may form a stable complex with DNA and interfere with the synthesis of DNA or RNA, thereby inhibiting the reproduction of bacteria. In addition to electrostatic effects, other interactions may also contribute to the antibacterial mode-of-action, such as chitosan-mediated chelation of metal ions.

**Antimicrobial Effect and Influencing Factors**

The antibacterial effect of chitosan is affected by different factors. Chitosan from different sources and in purity was used and reported in literatures, therefore, it is difficult to make a direct comparison. Besides the molecular weight and types of bacteria, the antibacterial properties of chitosan are largely affected by the degree of deacetylation, resulting in different densities of protonable amines. Other conditions such as the type and concentration of the solvent, pH value, and the metal ion strength of the environment will also affect the antibacterial properties of chitosan. The influencing factors have been elaborated in detail by Park et al. To improve the solubility and antibacterial effect of chitosan, many chitosan derivatives have been developed. Due to the reactivity differences of the primary amine and primary alcohols within chitosan, it is easy to obtain chitosan derivatives through modification.

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Quaternized chitosan shows not only good water solubility, but also moderate to strong antibacterial properties against bacteria and fungi. Mohamed et al. reported the minimum inhibitory concentration (MIC) of a series of quaternized chitosan against *Escherichia coli* (*E. coli*) to be 6–300 μg/mL. In order to improve the antibacterial activity, Chen et al. synthesized N-quaternary ammonium-O-sulfobetaine-chitosan. The quaternary ammonium group and sulfobetaine were introduced to improve antibacterial activity and biocompatibility of chitosan, respectively. Tang et al. incorporated quaternised chitosan derivatives (hydroxypropyltrimethyl ammonium chloride chitosan, HACC) in poly(methyl methacrylate) (PMMA) bone cement and showed that 26% HACC-loaded PMMA prevented biofilm formation of *Staphylococcus aureus* (*S. aureus*) and *E. coli* at the neutral pH. Másson et al. investigated the antibacterial structure-activity relationship of chitosan derivatives with different degrees of substitution on the 2-amino group of chitosan, N,N,N-trimethylamine, N-acetyl and N-stearyl, and identified the best substitution range.

Though quaternization is an effective strategy to increase the antibacterial activities of chitosan, the cell toxicity of quaternized chitosan remains a serious obstacle for biological applications such as antimicrobial biomaterials. Ma and Guo et al. synthesized quaternized chitosan grafted polyaniline (QCS-g-polyaniline) using oxidized dextran as the crosslinker, and developed a series of in situ forming antibacterial, conductive and degradable hydrogels called QCS-g-polyaniline hydrogels (Fig. 2). The results showed that the introduction of polyaniline into QCS could reduce the cytotoxicity of QCS and improve the antibacterial activity QCS. The antibacterial activities of the hydrogels with 3 wt% polyaniline were 95% and 90% against *E. coli* and *S. aureus*, respectively.

Some other derivatives were also explored, such as carboxymethyl chitosan, N-alkyl chitosan, N-benzyl chitosan, chitosan-sulfonamide derivatives, chitosan-g- aminoanthracene derivatives and urea-functionized chitosan derivatives with enhanced antibacterial activity. Kritchenkov et al. developed N-(3-azido-2-hydroxypropyl)chitosan that showed higher antibacterial activity than that of ampicillin and gentamicin. The finding implied potential application of chitosan in food coatings. Alkylated chitosan was also prepared under basic ionic liquid conditions and was found to show excellent antibacterial activity against *P. aeruginosa*.

In addition, nanoparticles of chitosan or chitosan derivatives showed high antibacterial activity, which may be attributed to the high positive charge density on the surface. Junginger et al. synthesized N-trimethyl chitosan nanoparticles and showed a high growth inhibitory on *S. aureus*. Maragoni et al. developed antimicrobial nanoparticles combining chitosan with rhamnolipid (Fig. 3a). With the addition of rhamnolipid, chitosan/rhamnolipid nanoparticles showed decreased size and dispersity index, a higher density of positive charge and a better antimicrobial activity against *S. aureus* than that of either single rhamnolipid or chitosan for both planktonic bacteria and biofilms. Omidi and Kakanejadifard developed new chitosan nanoparticles by grafting pyridinium salts on the surface (Fig. 3b) and these new nanoparticles showed good antibacterial activity against two types of Gram-positive bacteria: *S. aureus* and *Bacillus cereus* (*B. cereus)*.

**Chitosan and Chitosan Derivatives Grafted with Peptides and Polypeptides**

Inspired by peptidoglycan, a component of microbial cell wall, polysaccharides linked with peptides were proposed for antibacterial application.

**Chitosan grafted with short peptides**

Chitosan and antimicrobial peptides could be conjugated together via chemical bonds to form composite antimicrobial
Fan et al. synthesized complexes of nisin, a natural antimicrobial peptide and chitosan derivatives by combining nisin and chitosan via electrostatic action, and found the complex showed some antimicrobial effect. Subsequently, they grafted nisin onto hydroxypropyl chitosan (HPCS) to improve antimicrobial activity in a weakly acidic environment. Quaternary ammonium chitosan (QCS) with grafted polypeptides and chitosan complex, a copolymer of chitosan and polyllysine (CS-g-K16) to mimic peptidoglycan and polylysine (CS-PL). The effectiveness of the antimicrobial chitosan complexes was further verified by in vivo studies on animals. Du et al. explored the antimicrobial properties of self-assembled peptidopolysaccharides that were synthesized by grafting antimicrobial polypeptides to chitosan. The hollow structure of the nano-micelle assemblies could easily wrap drugs. Chan-Park et al. explored synthetic polypeptides and chitosan complex, a copolymer of chitosan and polyllysine (CS-g-K16) to mimic peptidoglycan components and found excellent antimicrobial activity and high selectivity. Cell wall wrinkling was observed on E. coli, Pseudomonas aeruginosa (P. aeruginosa), S. aureus, Candida

Fig. 3 (a) The scheme of C-NPs and C/RL-NPs synthesis (Reproduced with permission from Ref. [37]; Copyright (2020) American Chemical Society). (b) The synthesis of modified chitosan nanoparticle (Reproduced with permission from Ref. [38]; Copyright (2019) Elsevier).
Albicans (C. albicans) and Fusarium solani (F. solani) after microbes were treated with CS-g-K16. Short chitosan grafted with oligolysine chloride salt could self-assemble to nanoparticles and effectively inhibit MRSA growth by four orders of magnitude in a mouse excision wound model (Fig. 5b).\textsuperscript{[47]}

**Antimicrobial Application of Chitosan and Its Derivatives**

Chitosan and its derivatives can be used as antibacterial agents and preservatives in the food industry. Savvaidis \textit{et al.} reported chitosan can enhance the freshness of fish during storage.\textsuperscript{[48]}

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\textbf{Fig. 4} The structure of peptide-modified chitosan. (a) HPCS modified with nisin (Reproduced with permission from Ref. [41]; Copyright (2017) Elsevier). (b) QCS modified with nisin (Reproduced with permission from Ref. [42]; Copyright (2017) Taylor & Francis). (c) Schematic diagram of anoplin-chitosan conjugates (Helices: anoplin; black ribbon: linear chitosan polymer) (Reproduced with permission from Ref. [43] Copyright (2015) Royal Society of Chemistry).

\textbf{Fig. 5} The structure of peptide-modified chitosan. (a) ε-PL-grafted chitosan (Reproduced with permission from Ref. [44]; Copyright (2017) Royal Society of Chemistry). (b) Chitosan-graft-oligolysine chloride salt (Reproduced with permission from Ref. [47]; Copyright (2017) American Chemical Society). (c) Antibacterial peptide-grafted chitosan (Reproduced with permission from Ref. [45]; Copyright (2013) American Chemical Society). (d) Polylysine-grafted chitosan (Reproduced with permission from Ref. [46]; Copyright (2012) WILEY-VCH).
Chitosan-based films can be used as food packaging materials. Rhim et al. used chitosan and sulfur nanoparticles to prepare antibacterial composite films, taking advantage of sulfur nanoparticles’ antibacterial function. This composite membrane has a good antibacterial effect on E. coli and Listeria monocytogenes (L. monocytogenes) and can be used for food packaging. Siripatrawan et al. prepared nanocomposite of nanosized titanium dioxide and chitosan, with the ability of ethylene photocatalytic degradation and antibacterial effect on bacteria and fungi (Fig. 6a), which has potential as active packaging materials for post-harvest application. Lin et al. fixed nisin-loaded poly-y-glutamic acid/chitosan nanoparticles on PEO nanofibers as potential antibacterial packaging materials for food preservation, and tested the antibacterial effect on L. monocytogenes.

Chitosan and its derivatives are also widely studied as medical materials. Ji et al. constructed an antibacterial film via layer-by-layer assembly of heparin and chitosan, which showed the potential in surface modification of medical devices. Wang et al. developed a novel chitosan-based antibacterial hydrogel adhesive by integrating hydrocaffeic acid-modified chitosan (CS-HA) with hydrophobically modified chitosan lactate (hmCS lactate) (Fig. 7). The study suggested chitosan-based hydrogels as promising sutureless materials in surgery. Chitosan is also used in antibacterial surface materials, which has been discussed by Yu et al.

Chitosan is applied to wound dressings in various forms such as hydrogels, fibers, membranes and sponges. Tariq and Hasan et al. used chitosan-PEG-silver nitrate to prepare silver nanoparticle-based hydrogels that showed excellent antibacterial activity (Fig. 6c). Experiments have shown that this hydrogel can continuously release silver nanoparticles for at least seven days, which accelerates the healing of diabetic wounds. Guo et al. designed multifunctional injectable hydrogel dressing by mixing the N-carboxyethyl chitosan and oxidized hyaluronic acid-graft aniline tetramer (OHA-AT) polymer under physiological conditions. It can be used as a potential bioactive wound dressing for skin wound healing. Guo et al. synthesized quaternized chitosan-g-polyaniline and mixed with poly(ethylene glycol)-co-poly(glycerol sebacate) functionalized benzaldehyde group to obtain injectable hydrogel for wound dressings. Combining the favorable hemostatic effect and biocompatibility of chitosan, Guo and Ma et al. prepared an injectable shape memory hemostatic dressing, using carbon nanotubes and glycidyl methacrylate functionalized quaternized chitosan (QCSG/CNT) to possess antibacterial activity and blood absorptive capacity. Chan-Park et al. reported an antimicrobial hydrogel based on highly quaternized dimethyldecylammonium chitosan grafting with poly(ethylene glycol) methacrylate and poly(ethylene glycol) diacrylate, and proposed an “anionic sponges” antimicrobial mechanism, which attracts anionic phospholipids from bacterial cell membranes to the gel pores and eventually destroys the cell membrane to kill bacteria (Fig. 6b). Mandraccia et al. prepared chitosan-based hydrogels by crosslinking glycol chitosan with diepoxy PEG, and the obtained hydrogel displayed antibacterial activity against S. aureus and a pronounced pro-angiogenic activity, indicating potential application.

**Fig. 6** Antimicrobial application of chitosan and its derivatives. (a) Chitosan-TiO$_2$ nanocomposite film with antimicrobial activity and photocatalytic degradation (Reproduced with permission from Ref. [50]; Copyright (2018) Elsevier). (b) Schematic diagram of the anion sponge model and computer simulation of the killing mechanism (Reproduced with permission from Ref. [60]; Copyright (2011) Nature). (c) Preparation and application of chitosan-PEG-silver nitrate based hydrogel (Reproduced with permission from Ref. [56]; Copyright (2019) Elsevier). (d) Preparation and performance of PVA/chitosan/starch nanofiber mats (Reproduced with permission from Ref. [62]; Copyright (2019) Elsevier).
Fig. 7  (a) Polymer synthesis and hydrogel preparation and (b) *in vitro* anti-infective properties of hydrogel (Reproduced with permission from Ref. [53]; Copyright (2020) American Chemical Society).
tion as wound dressing materials.\cite{61}

In addition to hydrogels, electrospun fiber mats can be used as wound dressings due to the interconnected network, high surface area and designable porosity. Khorasani et al. used electrospinning to prepare PVA/chitosan/starch nanofiber mats and verified their mechanical properties, cell compatibility and antibacterial properties (Fig. 6d). These nanofiber mats can be used as a wound dressing to protect wounds from bacterial infections and effectively accelerate wound healing.\cite{62} Chen et al. developed a novel surface fluid-swellable chitosan fiber with better water absorption capacity and stronger antibacterial activities than chitosan fiber, which had great potential to be used as wound dressings.\cite{63}

Membrane is another important form for wound dressing. Bacterial cellulose chitosan membrane was prepared by immersing bacterial cellulose in chitosan, which can be used to treat wounds and has obvious growth inhibition effect on E. coli and S. aureus.\cite{64} Ren and Qiu et al. developed quaternary ammonium N-halamine chitosan (CSENDMH) based nanofibrous membranes, which offered antibacterial activity and hemostasis capability as potential wound dressings.\cite{65}

Chitosan and its derivatives are also applied to textile industry. Cotton fabric treated with carboxymethyl chitosan at 0.1% concentration showed good antimicrobial activity against E. coli and S. aureus.\cite{66} Novel core-shell particles consisting of poly(n-butyl acrylate) cores and chitosan shells were prepared and designed as an antibacterial coating for textiles. The cotton fabric treated with the particles confers excellent antibacterial property.\cite{67} Chitosan was added into the main chain polypolyurethanes which can improve antibacterial activity of polypolyurethanes. This synthesized chitosan-polypolyurethanes can be used as an antibacterial finishing with potential application in polyester/cotton textiles.\cite{68}

**Dextran**

Dextran, a polysaccharide composed of glucose as a monosaccharide, with glucose units connected by α-(1→6) glycosidic bonds, widely exists in microorganism, plant and animals. Dextran has attracted attentions owing to its advantages, such as water solubility, biocompatibility, biodegradability, immunomodulation and easy chemical modification.\cite{69} O’Connor et al. prepared dextran-polyallylamine (DexPAA) hydrogel which showed antibacterial activity.\cite{70} Nichifor et al. designed a series of cationic amphiphilic dextran derivatives, with a hydrophobic alkyl chain at the reduction end and a quaternary ammonium group on the main chain (Fig. 8). These researchers studied the effects of dextran molar mass, terminal alkyl chain length, and side chain quaternary ammonium salt structure on antimicrobial activity, and found that a proper balance between the hydrophobic and hydrophilic groups within the polymer has great influence on antibacterial activity.\cite{71} Aminlari et al. prepared lysozyme-dextran conjugate using Maillard reaction and found the conjugate reduced the number of E. coli in cheese curd by 3 log after 40 days storage.\cite{72} Dextran methacrylate (Dex-MA), a photo-crosslinking derivative of dextran, can mitigate bacterial biofilm. Hence, Haldar et al. synthesized antibacterial hydrogel by mixing the cationic biocide and Dex-MA to kill bacteria. The gel can remove the formed bacterial biofilm in vitro and in superficial skin infection.\cite{73} Li et al. grafted polypeptide to thiolated dextran via thiol-ene ‘click’ reaction and demonstrated effective therapeutic effects in a mouse model of sepsis.\cite{74}

**HYALURONIC ACID**

Hyaluronic acid (HA), a polysaccharide consisting of D-glucuronic acid and N-acetylg glucosamine, is an important component of extracellular matrix. HA has many important functions in the body, such as lubricating joints, regulating the permeability of blood vessel wall, promoting wound healing and moisturizing.\cite{75} Though HA has some activity of anti-adhesion and anti-biofilm of bacteria,\cite{76} further modifications are necessary to expand the application in antibacterial field. Xia and Zhang prepared antibacterial wound dressing by conjugating antimicrobial peptide Tet213 onto the substrates of alginate, hyaluronic acid, and collagen, to exhibit antimicrobial activity (Fig. 9a).\cite{77} Thebault et al. coupled nisin to HA and achieved antimicrobial activity against Gram-positive bacteria.\cite{78} To improve the mechanical strength and anti-infection ability of HA hydrogel, polydopamine (PDA) and sulfurized hyaluronic acid (HA-SH) were used (Fig. 9b).\cite{79} PDA endows HA hydrogel with good tissue adhesion, efficient free-radical scavenging and antibacterial ability for wound dressing application. Francolini and Piozzi fabricated chitosan (CS)-HA matrices as wound dressing, with HA incorporated into CS matrix at over 5% to reduce S. epidermidis fouling on CS matrix.\cite{80}

**Fig. 8** Synthesis of cationic amphiphilic dextran derivatives (Reproduced with permission from Ref. [71]; Copyright (2017) Elsevier).
CELLULOSE

Cellulose is the most widely distributed polysaccharide in nature. While cellulose itself has no antimicrobial activity, many researches have been done to enhance cellulose’s antimicrobial activity and application. Zhang et al. synthesized cellulose-based Schiff base through condensation of dialdehyde cellulose (DAC) with lysine (Fig. 10a), which showed higher antibacterial activity than DAC and potential application in papermaking. Anionic poly(ionic liquids) (PILs) were antimicrobial agents formed by choline and amino acids (AAs) and they were incorporated into the bacterial cellulose to fabricate composite membranes (Fig. 10b), which exhibited efficient antibacterial and antifungal activity, and good biocompatibility as a promising antibacterial wound dressing.

Zheng et al. prepared aminoalkyl-grafted bacterial cellulose membranes to have antibacterial properties (Fig. 10c). Liu et al. grafted nisin to 2,3-dialdehyde cellulose by Schiff base reaction, and the modified cellulose can be used as a food packaging material to extend shelf life of fresh pork owing to the packing material’s antimicrobial activity.

POLYSACCHARIDES FROM OTHER PLANTS OR ANIMALS

In addition to chitosan, dextran, HA, cellulose and their derivatives, there are other polysaccharides showing antibacterial activity as summarized in Table 1. These polysaccharides are

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mainly from medicinal plants. These polysaccharides could be explored as potential natural bacteriostatic agents in the food and pharmaceutical industries. However, the antibacterial mechanism of most these polysaccharides remains unclear.

CONCLUSIONS AND PERSPECTIVE

Multidrug-resistant microbial infection is emerging quickly all over the world, which has become a formidable challenge for public health globally. The drain of new antibiotic pipeline indicates the arrival of the era of post-antibiotics. Therefore, it is urgent to develop new antimicrobial agents with high-efficiency, favorable biocompatibility and low susceptibility for microorganisms to develop resistance. Polysaccharides exist widely in plants, animals and microorganisms and regulate various biological functions, including resistance to bacterial invasion and immune regulation. Therefore, polysaccharides and their derivatives have received extensive attention as potential antibacterial agents and have shown antibacterial properties. However, most researches are still in the conceptual and model study stage, and further exploration is necessary for both fundamental and practical studies. Polysaccharides have

Fig. 10  Antimicrobial materials based on cellulose. (a) Cellulose-based Schiff base through condensation of dialdehyde cellulose (DAC) with lysine (Reproduced with permission from Ref. [81]; Copyright (2020) Elsevier). (b) BC/PIL composite membranes (Reproduced with permission from Ref. [82]; Copyright (2020) American Chemical Society). (c) Aminoalkyl-grafted BC membranes (Reproduced with permission from Ref. [83]; Copyright (2020) WILEY-VCH).
obvious advantage of their easy availability from nature sources. Nevertheless, the structural complexity, batch-to-batch variation, immunogenicity concerns and infectious concerns associated with polysaccharides are obstacles for application, especially in biomedical fields.

BIOGRAPHY

Prof. Run-Hui Liu obtained PhD in Organic Chemistry working on carbohydrate synthesis in 2009 at Purdue University. Afterward, he joined Prof. Linda Hsieh-Wilson lab at California Institute of Technology as a postdoc researcher. In 2010, he moved to University of Wisconsin-Madison and worked as a postdoc in Prof. Samuel H. Gellman lab. In late 2014, he took a professor position in the School of Materials Science and Engineering at East China University of Science and Technology (ECUST). His current research focuses on polypeptides and peptide mimicking polymers for antimicrobial and tissue engineering applications.

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REFERENCES

1. Allegranzi, B.; Nejad, S. B.; Combescure, C.; Graafmans, W.; Attar, H.; Donaldson, L.; Pittet, D. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *The Lancet* 2011, 377, 228–241.
2. Worthington, R. J.; Melander, C. Combination approaches to combat multidrug-resistant bacteria. *Trends Biotechnol.* 2013, 31, 177–184.
3. Brown, E. D.; Wright, G. D. Antibacterial drug discovery in the resistance era. *Nature* 2016, 529, 336–343.
4. Tang, Q.; Song, P.; Li, J.; Kong, F.; Sun, L.; Xu, L. Control of antibiotic resistance in China must not be delayed: the current state of resistance and policy suggestions for the government, medical facilities, and patients. *BioSci. Trends* 2016, 10, 1–6.
5. Imberty, A.; Varrot, A. Microbial recognition of human cell surface glycoconjugates. *Curr. Opin. Struct. Biol.* 2008, 18, 567–576.
6. Bishop, J. R.; Gagné, P. Evolution of carbohydrate antigens--microbial forces shaping host glycemies? *Glycobiology* 2007, 17, 23R–34R.
Yu, Y.; Shen, M.; Song, Q.; Xie, J. Biological activities and pharmaceutical applications of polysaccharide from natural resources: a review. Carbohydr. Polym. 2018, 183, 91–101.

Perinelli, D. R.; Fagioli, L.; Campana, R.; Lam, J. K. W.; Baffone, W.; Palmieri, G. F.; Casettari, L.; Bonacucina, G. Chitosan-based nanosystems and their exploited antimicrobial activity. Eur. J. Pharm. Sci. 2018, 117, 8–20.

Li, Y. T.; Chen, B. J.; Wu, W. D.; Ge, K.; Wei, X. Y.; Kong, L. M.; Xie, Y. Y.; Gu, J. P.; Zhang, J. C.; Zhou, T. Antioxidant and antimicrobial evaluation of carboxymethylated and hydroxamated degraded polysaccharides from Sargassum fusiforme. Int. J. Biol. Macromol. 2018, 118, 1550–1557.

No, H. K.; Park, N. Y.; Lee, S. H.; Meyers, S. P. Antibacterial activity of chitosan and chitosan oligomers with different molecular weights. Int. J. Food Microbiol. 2002, 74, 65–72.

Synowiecki, J.; Al-Khateeb, N. A. Production, properties, and some new applications of chitin and its derivatives. Crit. Rev. Food Sci. Nutr. 2003, 43, 145–171.

Muzzarelli, R. A. A. Chitins and chitosans for the repair of wounded skin, nerve, cartilage and bone. Carbohydr. Polym. 2009, 76, 167–182.

Peng, X. H.; Zhang, L. Surface fabrication of hollow microspheres from N-methylated chitosan cross-linked with gutaraldehyde. Langmuir 2005, 21, 1091–1095.

Allan, C. R.; Hadwiger, L. A. The fungidal effect of chitosan on fungi of varying cell wall composition. Exp. Mycol. 1979, 3, 285–287.

Palma-Guerrero, J.; Lopez-Jimenez, J. A.; Perez-Bernà, A. J.; Huang, I. C.; Jansson, H. B.; Salinas, J.; Villalain, J.; Read, N. D.; Lopez-Urraca, L. V. Membrane fluidity determines sensitivity of filamentous fungi to chitosan. Mol. Microbiol. 2010, 75, 1021–1032.

Young, D. H.; Kohle, H.; Kaus, H. Effect of chitosan on membrane permeability of suspension-cultured glyceine max and phaseolus vulgaris cells. Plant Physiology 1982, 70, 1449–1454.

Helander, I. M.; Nurmi-Haasla, E. L.; Ahvenainen, R.; Rhodeas, J.; Roller, S. Chitosan disrupts the barrier properties of the outer membrane of Gram-negative bacteria. Int. J. Food Microbiol. 2001, 71, 235–244.

Muzzarelli, R.; Jeuniaux, C.; Gooday, G. W. Chitin in nature and technology. Springer US, New York, 1986.

Krajewska, B.; Wydro, P.; Jańczyk, A. Probing the modes of antibacterial activity of chitosan. Effects of pH and molecular weight on chitosan interactions with membrane lipids in langmuir films. Biomacromolecules 2011, 12, 4144–4152.

Rabea, E. I.; Badawy, M. E. T.; Stevens, C. V.; Hoftte, M.; Steurbaut, W.; Smagghe, G. Insecticidal and fungicidal activity of new synthesized chitosan derivatives. Pest Manage. Sci. 2005, 61, 951–960.

Dragostin, O. M.; Samal, S. K.; Dash, M.; Lupascu, F.; Panzaruiu, A.; Tchilins, C.; Ghetu, N.; Danciu, M.; Dubreul, P.; Pieptu, D.; Vasile, C.; Tatia, R.; Profire, L. New antimicrobial chitosan derivatives for wound dressing applications. Carbohydr. Polym. 2016, 141, 28–40.

Prichystalova, H.; Almonasy, N.; Abdel-Mohsen, A. M.; Abdel-Rahman, R. M.; Fouda, M. M.; Voitova, L.; Kobera, L.; Spotz, Z.; Burgert, L.; Jancar, J. Synthesis, characterization and antibacterial activity of new fluorescent chitosan derivatives. Int. J. Biol. Macromol. 2014, 65, 234–240.

Zhang, J.; Tan, W.; Wei, L.; Chen, Y.; Mi, Y.; Sun, X.; Li, Q.; Dong, F.; Guo, Z. Synthesis of urea-functionalized chitosan derivatives for potential antifungal and antioxidant applications. Carbohydr. Polym. 2019, 215, 108–118.

Kritchenvkov, A. S.; Egorov, A. R.; Kurasova, M. N.; Volkova, O. V.; Meledina, T. V.; Lipkan, N. A.; Tskhovrebov, A. G.; Kurluk, A. V.; Shakola, T. V.; Dins, A. P.; Egorov, M. Y.; Savicheva, E. A.; Dos Santos W. M. Novel non-toxic high efficient antibacterial azido chitosan derivatives with potential application in food coatings. Food Chem. 2019, 301, 125247.

Pei, L.; Cai, Z.; Shang, S.; Song, Z. Synthesis and antibacterial activity of alkyloxyl chitosan under basic ionic liquid conditions. J. Appl. Polym. Sci. 2014, 131, 2540–2540.

Sadeghi, A. M. M.; Dorkoosh, F. A.; Avadil, M. R.; Saadat, P.; Rafiee-Tehrani, M.; Junginger, H. E. Preparation, characterization and antibacterial activities of chitosan, N-trimethyl chitosan (TMC) and N-diethlymethyl chitosan (DEMC) nanoparticles loaded with insulin using both the ionotropic gelation and polyelectrolyte complexation methods. Int. J. Pharm. 2008, 355, 299–306.

Marangoz, C. A.; Martins, V. C. A.; Ling, M. H.; Melo, C. C.; Plepis, A. M. G.; Meyer, R. L.; Nitschke, M. Combination of rhamnolipid and chitosan in nanoparticles boosts their antimicrobial efficacy. ACS Appl. Mater. Interfaces 2020, 12, 5488–5499.

Omidi, S.; Kakanajedifard, A. Modification of chitosan and chitosan nanoparticle by long chain pyridinium compounds: synthesis, characterization, antibacterial, and antioxidant activities. Carbohydr. Polym. 2019, 208, 477–485.

Martin, I.; Ruyschaert, J. M.; Sanders, D.; Giffard, C. J. Interaction of the lambitoxic nisin with membranes revealed by fluorescence quenching of an introduced tryptophan. Eur. J. Biochem. 1996, 239, 156–164.

Cai, J.; Yang, J.; Wang, C.; Hu, Y.; Lin, J.; Fan, L. Structural characterization and antimicrobial activity of chitosan (CS-40)/nisin complexes. J. Appl. Polym. Sci. 2010, 116, 3702–3707.

Zhu, C.; Zou, S.; Rao, Z.; Min, L.; Liu, M.; Liu, L.; Fan, L. Preparation of nisin modified chitosan-loaded PMMA nanoparticles for dual drug delivery. Biomacromolecules 2012, 13, 365–377.
and characterization of hydroxypropyl chitosan modified with nisin. *Int. J. Biol. Macromol.* 2017, 105, 1017−1024.

42 Min, L.; Liu, M.; Zhu, C.; Liu, L.; Rao, Z.; Fan, L. Synthesis and in vitro antimicrobial and antioxidant activities of quaternary ammonium chitosan modified with nisin. *J. Biomater. Sci. Polym. Eng.* 2017, 28, 2034−2052.

43 Sahariah, P.; Sorensen, K. K.; Hjalmarssdottr, M. A.; Sigurjonsson, O. E.; Jensen, K. J.; Masson, M.; Thysegen, M. B. Antimicrobial peptide shows enhanced activity and reduced toxicity upon grafting to chitosan polymers. *Chem. Commun.* 2015, 51, 11611−11614.

44 Su, Y.; Tian, L.; Yu, M.; Gao, Q.; Wang, D.; Xi, Y.; Yang, P.; Lei, B.; Ma, P. X.; Li, P. Cationic peptidepolysaccharides synthesized by ‘click’ chemistry with enhanced broad-spectrum antimicrobial activities. *Polym. Chem.* 2017, 8, 3788−3800.

45 Zhou, C.; Wang, M.; Zou, K.; Chen, J.; Zhu, Y.; Du, J. Antibacterial polypeptide-grafted chitosan-based nanocapsules as an “armed” carner of anticancer and antiepileptic drugs. *ACS Macro Lett.* 2013, 2, 1021−1025.

46 Li, P.; Zhou, C.; Ratnapisheh, S.; Ye, K.; Poon, Y. F.; Hammond, P. T.; Duan, H.; Chan-Park, M. B. Cationic peptidepolysaccharides show excellent broad-spectrum antimicrobial activities and high selectivity. *Adv. Mater.* 2012, 24, 4130−4137.

47 Hou, Z.; Shankar, Y. V.; Liu, Y.; Ding, F.; Subramanian, J. L.; Ravikumar, V.; Zamudio-Vazquez, R.; Keogh, D.; Lim, H.; Tay, M. Y. F.; Bhattacharjya, S.; Rice, S. A.; Shi, J.; Duan, H.; Liu, X. W.; Mu, Y.; Tan, N. S.; Tam, K. C.; Pethe, K.; Chan-Park, M. B. Nanoparticles of short cationic peptidepolysaccharide self-assembled by hydrogen bonding with antibacterial effect against multidrug-resistant bacteria. *ACS Appl. Mater. Interfaces* 2017, 9, 38288−38303.

48 Tsiligiani, M.; Papavergou, E.; Soultos, N.; Magra, T.; Savvaaidis, I. N. Effect of chitosan treatments on quality parameters of fresh fish. *Int. J. Food Microbiol.* 2012, 159, 101−106.

49 Shankar, S.; Rhim, J. W. Preparation of sulfur nanoparticle-incorporated antimicrobial chitosan films. *Food Hydrocolloids* 2018, 82, 116−123.

50 Siripatrawan, U.; Kaewklin, P. Fabrication and characterization of chitosan-titanium dioxide nanocomposite film as ethylene scavenging and antimicrobial active food packaging. *Food Hydrocolloids* 2018, 84, 125−134.

51 Cui, H.; Wu, J.; Li, C.; Lin, L. Improving anti-listeria activity of cheese packaging via nanofiber containing nisin-loaded nanoparticles. *LWT–Food Sci. Technol.* 2017, 81, 233−242.

52 Fu, J.; Ji, J.; Yuan, W.; Shen, J. Construction of anti-adhesive and antibacterial multilayer films via layer-by-layer assembly of heparin and chitosan. *Biomaterials* 2005, 26, 6684−6692.

53 Du, X.; Liu, Y.; Yan, H.; Rafique, M.; Li, S.; Shan, X.; Wu, L.; Qiao, M.; Kong, D.; Wang, L. Anti-infective and pro-coagulant chitosan-based hydrogel tissue adhesive for sutureless wound closure. *Biomacromolecules* 2020, 21, 1243−1253.

54 Yu, Q.; Chen, H. Smart antibacterial surfaces with switchable function to kill and release bacteria. *Acta Polymearia Sinica* (in Chinese) 2020, 51, 319−325.

55 Wei, T.; Yu, Q.; Chen, H. Responsive and synergistic antibacterial coatings: fighting against bacteria in a smart and effective way. *Adv. Healthcare Mater.* 2019, 8, e1801381.

56 Masood, N.; Ahmed, R.; Tarig, M.; Ahmed, Z.; Masoud, M. S.; Ali, I.; Ashgar, R.; Andleeb, A.; Hasan, A. Silver nanoparticle impregnated chitosan-PEG hydrogel enhances wound healing in diabetes induced rabbits. *Int. J. Pharm.* 2019, 559, 23−36.

57 Qu, J.; Zhao, X.; Liang, Y.; Xu, Y.; Ma, P. X.; Guo, B. Degradable conductive injectable hydrogels as novel antibacterial, anti-

oxidant wound dressings for wound healing. *Chem. Eng. J.* 2019, 362, 549−560.

58 Zhao, X.; Wu, H.; Guo, B.; Dong, R.; Qiu, Y.; Ma, P. X. Antibacterial anti-oxidant electroactive injectable hydrogel as self-healing wound dressing with hemostasis and adhesiveness for cutaneous wound healing. *Biomaterials* 2017, 122, 34−47.

59 Zhao, X.; Guo, B.; Wu, H.; Liang, Y.; Ma, P. X. Injectable antibacterial conductive nanocomposite cryogels with rapid shape recovery for noncompressible hemorrhage and wound healing. *Nat. Commun.* 2018, 9, 2784.

60 Li, P.; Poon, Y. F.; Li, W.; Zhu, H. Y.; Yeap, S. H.; Cao, Y.; Qi, X.; Zhou, C.; Lamrani, M.; Beuerman, R. W. A polycationic antimicrobial and biocompatible hydrogel with microbe membrane suctioning ability. *Nat. Mater.* 2011, 10, 149−156.

61 Tripodo, G.; Trapani, A.; Rosato, A.; Di Franco, C.; Tamma, R.; Trapani, G.; Ribatti, D.; Mandracchia, D. Hydrogels for biomedical applications from glycol chitosan and PEG diglycidyl ether exhibit pro-angiogenic and antibacterial activity. *Carbohydr. Polym.* 2018, 198, 124−130.

62 Adeli, H.; Khorasani, M. T.; Parvazinia, M. Wound dressing based on electrospun PVA/chitosan/starch nanofibrous mats: fabrication, antibacterial and cytocompatibility evaluation and in vitro healing assay. *Int. J. Biol. Macromol.* 2019, 122, 238−254.

63 Xia, G.; Lang, X.; Kong, M.; Cheng, X.; Liu, Y.; Feng, C.; Chen, X. Surface fluid-swellable chitosan fiber as the wound dressing material. *Carbohydr. Polym.* 2016, 136, 860−866.

64 Lin, W. C.; Lien, C. C.; Yeh, H. J.; Yu, C. M.; Hsu, S. H. Bacterial cellulose and bacterial cellulose-chitosan membranes for wound dressing applications. *Carbohydr. Polym.* 2013, 94, 603−611.

65 Yin, M.; Wang, Y.; Zhang, Y.; Ren, X.; Qiu, Y.; Huang, T. S. Novel quaternized N-halamine chitosan and polyvinyl alcohol nanofibrous membranes as hemostatic materials with excellent antibacterial properties. *Carbohydr. Polym.* 2020, 232, 115823.

66 Gupta, D.; Haile, A. Multifunctional properties of cotton fabric treated with chitosan and carboxymethyl chitosan. *Carbohydr. Polym.* 2007, 69, 164−171.

67 Ye, W.; Leung, M. F.; Xin, J.; Kwong, T. L.; Lee, D. K. L.; Li, P. Novel core-shell particles with poly(n-butyl acrylate) cores and chitosan shells as an antibacterial coating for textiles. *Polymer* 2005, 46, 10538−10543.

68 Arshad, N.; Zia, K. M.; Jabeen, F.; Anjum, M. N.; Akram, N.; Zuber, M. Synthesis, characterization of novel chitosan based water dispersible polyurethanes and their potential deployment as antibacterial textile finish. *Int. J. Biol. Macromol.* 2018, 111, 485−492.

69 Huang, G.; Huang, H. Application of dextran as nanoscale drug carriers. *Nanomedicine* 2018, 13, 3149−3158.

70 O’Connor, N. A.; Abgharbieh, A.; Yasmeen, F.; Buabeng, E.; Mathew, S.; Samaroo, D.; Cheng, H. P. The crosslinking of polysaccharides with polyamines and dextran-polyallylamine antibacterial hydrogels. *Int. J. Biol. Macromol.* 2015, 72, 88−93.

71 Tuchilus, C. G.; Nichifor, M.; Mocanu, G.; Stanciu, M. C. Antimicrobial activity of chemically modified dextran derivatives. *Carbohydr. Polym.* 2017, 161, 181−186.

72 Amiri, S.; Ramezani, R.; Aminlari, A. M. Antibacterial activity of dextran-conjugated lysosome against *Escherichia coli* and *Staphylococcus aureus* in cheese curd. *J. Food Prot.* 2008, 71, 411−415.

73 Hoque, J.; Haldar, J. Direct synthesis of dextran-based antibacterial hydrogels for extended release of biocides and eradication of topical biofilms. *ACS Appl. Mater. Interfaces* 2017, 9, 15975−15985.

74 Chen, Y.; Yu, L.; Zhang, B.; Feng, W.; Xu, M.; Gao, L.; Liu, N.; Wang, Q.; Huang, X.; Li, P.; Huang, W. Design and synthesis of biocompatible, hemocompatible, and highly selective
antimicrobial cationic peptidopolysaccharides via click chemistry. *Biomacromolecules* 2019, 20, 2230–2240.
75 Radaeva, I. F.; Kostina, G. A.; Zmeskall, A. V. Hyaluronic acid: biological role, structure, synthesis, isolation, purification, and applications. *Appl. Biochem. Microbiol.* 2013, 39, 111–115.
76 Drago, L.; Cappelletti, L.; de Vecchi, E.; Pignatari, L.; Torretta, S.; Mattina, R. Antiadhesive and antibiofilm activity of hyaluronic acid against bacteria responsible for respiratory tract infections. *APMIS* 2014, 122, 1013–1019.
77 Lin, Z.; Wu, T.; Wang, W.; Li, B.; Wang, M.; Chen, L.; Xia, H.; Zhang, T. Biofunctions of antimicrobial peptide-conjugated alginate/hyaluronic acid/collagen wound dressings promote wound healing of a mixed-bacteria-infected wound. *Int. J. Biol. Macromol.* 2019, 140, 330–342.
78 Lequeux, I.; Ducasse, E.; Jouenne, T.; Thebault, P. Addition of antimicrobial properties to hyaluronic acid by grafting of antimicrobial peptide. *Eur. Polym. J.* 2014, 51, 182–190.
79 Yu, Q. H.; Zhang, C. M.; Jiang, Z. W.; Qin, S. Y.; Zhang, A. Q. Mussel-inspired adhesive polydopamine-functionalized hyaluronic acid hydrogel with potential bacterial inhibition. *Glob. Chall.* 2020, 4, 1900068.
80 Silvestro, I.; Lopreaiato, M.; Scotto d’Abusco, A.; di Lisio, V.; Martinelli, A.; Pizzi, A.; Francolini, I. Hyaluronic acid reduces bacterial fouling and promotes fibroblasts’ adhesion onto chitosan 2D-wound dressings. *Int. J. Mol. Sci.* 2020, 21, 2070.
81 Zhang, L.; Yan, P.; Li, Y.; He, X.; Dai, Y.; Tan, Z. Preparation and antibacterial activity of a cellulose-based Schiff base derived from dialdehyde cellulose and L-lysine. *Ind. Crops Prod.* 2020, 145, 112126.
82 He, X.; Yang, Y.; Song, H.; Wang, S.; Zhao, H.; Wei, D. Polyanionic composite membranes based on bacterial cellulose and amino acid for antimicrobial application. *ACS Appl. Mater. Interfaces* 2020, 12, 14784–14796.
83 He, W.; Zhang, Z.; Zheng, Y.; Qiao, S.; Xie, Y.; Sun, Y.; Qiao, K.; Feng, Z.; Wang, X.; Wang, J. Preparation of aminooaryl-grated bacterial cellulose membranes with improved antimicrobial properties for biomedical applications. *J. Biomed. Mater. Res. A* 2020, 108, 1086–1098.
84 Wu, Y.; Li, Q.; Zhang, X.; Li, Y.; Li, B.; Liu, S. Cellulose-based peptidopolysaccharides as cationic antimicrobial package films. *Int. J. Biol. Macromol.* 2019, 128, 673–680.
85 Palanisamy, S.; Vinosh, M.; Muradhupandi, T.; Rajasekar, P.; Prabhu, N. M. In vitro antioxidant and antibacterial activity of sulfated polysaccharides isolated from *Spatoglossum asperum*. *Carbohydr. Polym.* 2017, 170, 296–304.
86 Zhu, H.; Sheng, K.; Yan, E.; Qiao, J.; Lv, F. Extraction, purification and antibacterial activities of a polysaccharide from spent mushroom substrate. *Int. J. Biol. Macromol.* 2012, 50, 840–843.
87 Meng, Q.; Li, Y.; Xiao, T.; Zhang, L.; Xu, D. Antioxidant and antibacterial activities of polysaccharides isolated and purified from *Diaphagma juglandis* fructus. *Int. J. Biol. Macromol.* 2017, 105, 431–437.
88 Ma, Y. L.; Zhu, D. Y.; Thakur, K.; Wang, C. H.; Wang, H.; Ren, Y. F.; Zhang, J. G.; Wei, Z. J. Antioxidant and antibacterial evaluation of polysaccharides sequentially extracted from onion (*Allium cepa* L). *Int. J. Biol. Macromol.* 2018, 111, 92–101.
89 Li, X. L.; Thakur, K.; Zhang, Y. Y.; Tu, X. F.; Zhang, Y. S.; Zhu, D. Y.; Zhang, J. G.; Wei, Z. J. Effects of different chemical modifications on the antibacterial activities of polysaccharides sequentially extracted from peony seed dreg. *Int. J. Biol. Macromol.* 2018, 116, 664–675.
90 Wang, Z.; Xue, R.; Cui, J.; Wang, J.; Fan, W.; Zhang, H.; Zhan, X. Antibacterial activity of a polysaccharide produced from *Chaetomium globosum* CGMCC 6882. *Int. J. Biol. Macromol.* 2019, 125, 376–382.
91 Wang, H. B. Cellulase-assisted extraction and antibacterial activity of polysaccharides from the dandelion *Taraxacum officinale*. *Carbohydr. Polym.* 2014, 103, 140–142.
92 Lu, H.; Gao, Y.; Shan, H.; Lin, Y. Preparation and antibacterial activity studies of degraded polysaccharide selenide from *Enteromorpha prolifera*. *Carbohydr. Polym.* 2014, 107, 98–102.
93 Vishwakarma, J.; Vavilala, S. L. Evaluating the antibacterial and biofilm inhibition potential of sulphated polysaccharides extracted from green algae *Chlamydomonas reinhardtii*. *J. Appl. Microbiol.* 2019, 127, 1004–1017.
94 Khuslov, I.; Avdeeva, E.; Shupletsova, V.; Khazikhamtova, Q.; Litvinova, L.; Porokhova, E.; Reshetov, Y.; Zvereva, I.; Mushkotovata, L.; Karpova, M.; Guryev, A.; Sukhodolo, I.; Belousov, M. Comparative in vitro evaluation of antibacterial and osteogenic activity of polysaccharide and flavonoid fractions isolated from the leaves of *Saussurea controversa*. *Molecules* 2019, 24, 3680.
95 Hajji, M.; Hamdi, M.; Sellimi, S.; Ksouda, G.; Laouer, H.; Li, S.; Nasri, M. Structural characterization, antioxidant and antibacterial activities of a novel polysaccharide from *Periploca laevigata* root barks. *Carbohydr. Polym.* 2019, 206, 380–388.
96 Wang, C. S.; Sun, Z.; Liu, Y.; Zheng, D.; Liu, X.; Li, S. Earthworm polysaccharide and its antibacterial function on plant-pathogen microbes in vitro. *Eur. J. Soil Biol.* 2007, 43, S135–S142.