

# Advances in Polysaccharide-Based Antimicrobial Delivery Vehicles



Vaishali Pawar, M. C. Bavya, K. Vimal Rohan, and Rohit Srivastava

**Abstract** Antimicrobial resistance is one of the major causes for morbidity and mortality in sepsis patients. Trying to circumvent the challenge with newer antibiotics has led to the drug misuse and bacterial recalcitrance. Recently, polysaccharides have proffered inexplicable contributions in the field of antimicrobial drug delivery. Structural hierarchy and tunability in biochemical and mechanical properties make polysaccharides unique. Some of the polysaccharides in the naïve state itself pose antimicrobial properties in inhibiting bacterial colonization via blocking carbohydrate receptor associated with host–bacterial responses. While, rest of the saccharides upon modification delivers antibacterial drugs onto targeted sites with sustained or burst release depending upon the need. Ongoing research keeps pace in promoting polysaccharides for local as well as systemic therapy due to its attractive features, mainly biocompatibility, mechanical strength, stimuli responsiveness, protein affinity and reduced toxicity. This chapter presents the updates of prominent polysaccharides involved in the field of antimicrobial drug delivery.

**Keywords** Polysaccharide · Antimicrobial · Drug delivery · Antibiotic resistance · Biocompatibility · Biomaterial

## Introduction

Recent developments in the field of biomaterial science and regenerative medicine have led to innovations in the development of “bioactive materials” capable of producing biological responses, especially in the area of antimicrobial applications. Of

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particular significance, the materials meant for orthopedic and other implant-related infections should have the ability to defend against microbial invasions and produce a favorable environment for bone regeneration.

Typically, after orthopedic procedures or implant fixation, cells grow onto an implant and further upon the appropriate conditions, the proteins and cells envelop the implant. The major challenge here is material acceptance and a plausible risk of microbial growth, which may further elicit negative responses and pave the way for rejection of the implant or give rise to infections. Therefore, it is of the foremost importance to treat orthopedic implant-associated disorders with biocompatible materials for minimizing such complications [1].

The etiology behind purulent bacterial infections is due to the recalcitrant behavior of bacteria upon drug exposure, developing resistance toward antibiotics [2]. A recent report suggests that implant-associated infections and the subsequent risk of causing morbidity and mortality are on the rise and have to be addressed quickly [3]. Generally, infections are treated using systemic antibiotics, debridement therapy, implant removal, and complicated surgeries, which may require long-term rehabilitation procedures [4, 5]. In such cases, there is a considerable rise in capital, without guaranteeing a successful clinical outcome [6, 7]. However, the persistent growth of microorganisms and their genetic mutation has led to newer alternative research on the modification of existing drug delivery vehicles [8]. The selection of biomaterials is based on their innate antimicrobial activity or having the capability to imbibe antibacterial activity upon tuning their chemistry. Also, the ability to mimic the extracellular matrix and cause minimal harm to tissues may be considered for their use as carrier vehicles in medical sciences to treat antimicrobial infections related to orthopedic applications [9].

Solution for these life-intimidating complications is in developing biopolymeric antimicrobial drug delivery carriers or coatings, which could promote adequate bone tissue linkage. A novel approach amongst biopolymers is the use of polysaccharide carriers, which have equipped the ability to mimic the extracellular matrix, capability of tailoring their properties for improving antimicrobial properties, and ample biocompatibility with an ease of tuning surface functionalities to serve as an antimicrobial aid for bone and implant applications.

To define polysaccharides, it is important to know that they are biomaterials belonging to the class of simple sugars, derived from monosaccharides via glycosidic linkages, which are of significant research interest globally [10]. To put it into simpler terms, polysaccharides are hefty molecules originated from the Greek word “Poly” meaning many and “Saccharide” meaning sweet [11]. Polysaccharides can be chemically modified based on their reactive groups and structural diversity into functional and structural components of cells (glycoproteins, glycolipids); they are also capable of serving as a storage depot (glycogen) (Table 1) [12].

These characteristics of polysaccharides have led them to establish the field of drug delivery. Polysaccharides also serve as excellent antimicrobial agents due to the presence of functional groups (amine, aldehyde, carboxyl, and hydroxyl). The ease of tailoring them for more specific microbial targeting has made them suitable for use as antimicrobial agents [13]. Polysaccharides (like chitosan and alginate) exhibit inherent bioactivity with good cytocompatibility, degradability, miscibility,

**Table 1** Widely used polysaccharides, their classification, composition, availability, and functions

Polysaccharides	Classifications	Components	Availability	Function
Glucose	Homo	Primary monosaccharide	Plants, algae	Energy
Heparin	Hetero	D-glucuronic acid, N-sulpho D-glucosamine, L-iduronic acid	Blood, mast cells	Anticoagulant
Glycogen	Homo	Glucose	Liver, muscles	Storage depot
Starch	Homo	Glucose	Grains, vegetables	Paper manufacturing, textiles
Hyaluroic acid	Hetero	D-glucuronic acid, N-acetyl D-glucosamine	Skin, connective tissue	Shock absorber, lubricant
Alginate	Homo	D-mannuronate	Algae	Wound dressings
Chitosan	Homo	L-glucuronate	Crustacean, mushrooms	Wound dressings, hemostatic
Dextran	Homo	$\alpha$ -D-glucopyranosyl of sucrose	Bacteria	Nutrition, fermentation
Cellulose	Homo	Glucose	Basic structure in plant, vegetables, cells, wood,	Paper, plastics, explosives, photographic films
Pectin	Hetero	Homogalacturonan, Rhamnogalacturonan	Fruit extract, component of cell wall of many plants	Preparation of jam, jelly and flavoring agent
Chondroitin sulfate	Hetero	D-glucuronic acid, N-acetyl D-galactosamine-O- Sulfate	Cartilage	Bone-cartilage formation, cartilage accumulation

antioxidant, antitumor, antiviral, and antimicrobial activity [14, 15]. Additionally, other polysaccharides upon surface modification have proved to be excellent antibacterial carriers for delivering drugs [15, 16].

This chapter discusses how polysaccharides are tuned for antimicrobial drug delivery applications, and provides in-depth knowledge about widely used polymers in surgical site wounds and orthopedic implant-associated applications (such as alginate, chitosan, carrageenan, dextran, guar gum, hyaluronic acid, cellulose, and pectin).

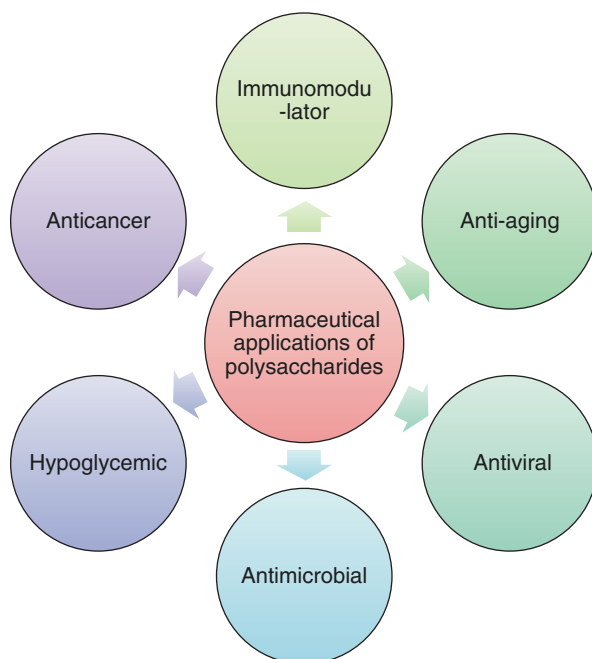
## Overview of Polysaccharides as Biological Macromolecules

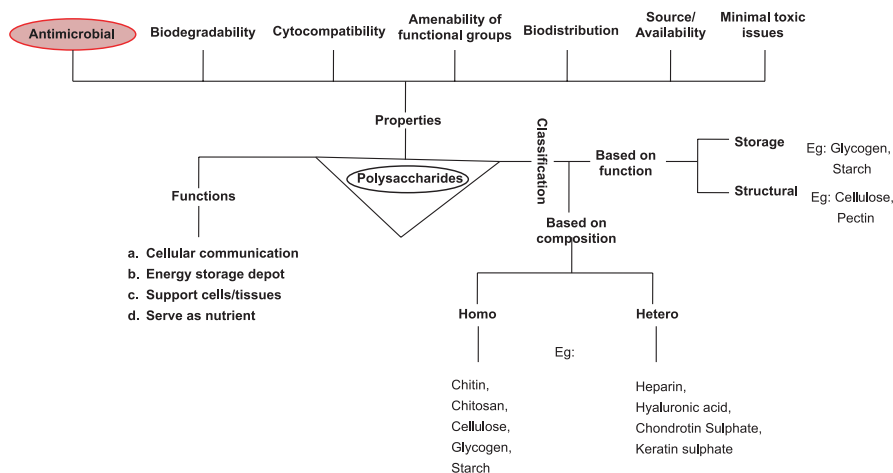
Carbohydrate-based polysaccharides are of paramount importance and have been eye-catching due to their contribution as drug delivery vehicles and their pivotal role in biomolecular recognition. The structure of polysaccharides can be linear or highly branched, having a general formula of  $C_x(H_2O)_y$  wherein  $x$  can vary from 200

to 2500 [17]. Physicochemical properties of polysaccharides are manipulated using intermolecular H-bonding associations and chain conformations. Owing to the presence of abundant hydroxyl groups in the repeating units of polysaccharides, inter- and intramolecular H-bonding occur easily, which imparts insolubility after drying, one of the required properties for gel and film formation. Polysaccharides are mostly present in helical conformations in solution form, and their stability depends upon the ionic concentration and temperature of the solution [18].

Polysaccharides are considered to be the most abundant biological macromolecules present in nature. They are distributed widely in plants, algae, fungi, microorganisms, and animals [19]. These biological macromolecules play an important role in various physiological functions of life. Several decades ago, polysaccharides found their use in pharmaceuticals, foodstuff, biomaterials and biofuels, and now due to the growing interest and deeper investigations, it is being proved that the value of polysaccharides in several novel bio applications is vast [20]. Of their important medical applications (Fig. 1), antimicrobial, anticancer, antiaging, and antiviral, as well as their role in immunomodulator, antioxidant, and being hypoglycemic are some of the indispensable applications proven by polysaccharides in biomedical science [17, 21]. Among the class of polysaccharides,  $\beta$ -glucans have been clinically tested for antitumor activity [22], which is a polysaccharide extracted from *Ganoderma lucidum* [23] and lentinans [24]. Many naturally occurring polysaccharides have been reported to possess antiviral, particularly anti-herpes, anti-influenza, and anti-HIV activity [22]. Cellulose, hemicellulose, and lignin can stimulate bowel movement, aid in preventing diverticulosis and hemorrhoids.

**Fig. 1** Important medical applications of polysaccharides



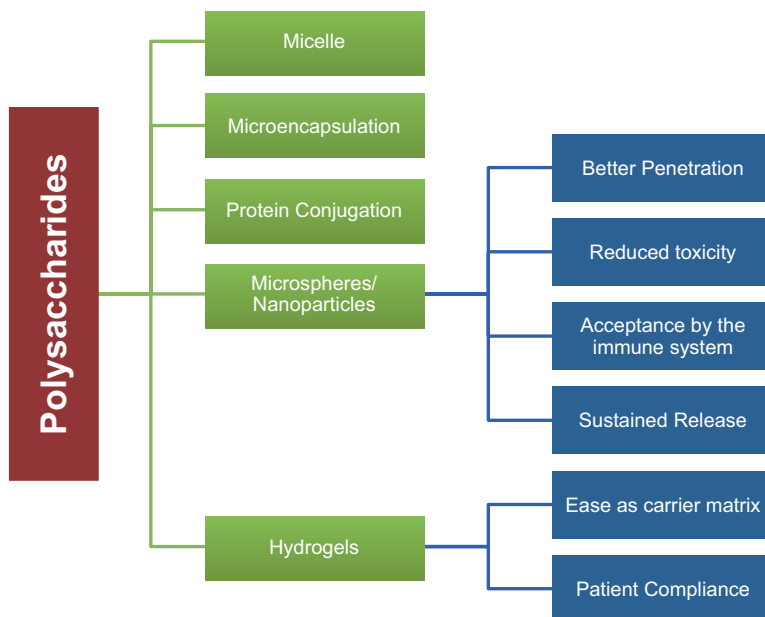


**Fig. 2** Overview of polysaccharides as biological macromolecules

However, the use of cellulose materials is restricted due to the absence of enzymes in the human body for its degradation. Few amongst the most commonly used polysaccharides are chitosan, alginate, starch, gelatin, cellulose, pectin, and dextran. According to study reports, it could be a combination of polysaccharides, that produces a desirable impact in biological applications rather than a single polysaccharide [18]. Hence, a blend of two or more polysaccharides has been prepared to develop biomaterials having necessary properties. Likewise, polysaccharides are also manipulated to blend with synthetic polymers. The optimization/tailoring of synthetic polymers is often completed to improve its suitability to find uses in biomedical applications. An overview of the use of polysaccharides as novel biological macromolecules is represented in Fig. 2.

## Polysaccharides as Drug Delivery Vehicles

Drug delivery or delivering drugs is defined as the distribution of therapeutically active molecules with certain approaches, formulations, and technologies inside the body to achieve a required therapeutic response with improved safety profiles. Fast changing trends in the global market scenario has contributed toward challenges in product development and technology, for the potential growth of pharmaceutical industries. However, in the current practice, bio-based materials have gained tremendous attention to be engineered as modified drug delivery vehicles [25]. Polysaccharides are of special interest, due to their unique properties such as stability, easy availability, non-toxicity, etc. and the ease of tailoring their end functional groups has allowed them to be a suitable candidate for drug delivery [26]. Moreover, the merit is in the customization or modification of polysaccharides chemically and



**Fig. 3** The way in which polysaccharides can be modified to find use in biomedical applications

biochemically marking them as an appropriate carrier in the field of drug delivery. The advantageous properties of polysaccharides allow their use in drug delivery especially to target organs/tissues with different delivery routes and with variable release profiles [27–29].

Figure 3 explains the way in which polysaccharides have been modified to find multiple uses in biomedical applications. Polysaccharides can be formulated as nanoparticles, microparticles, monoliths, hydrogels, sponges, and beads to incorporate drugs. In drug delivery systems, drug loading is an important parameter when concerned with pharmaceutical formulations, wherein they are largely correlated with a matrix structure, surface area, and porosity of the polysaccharides [30]. Tuning the surface modification of polysaccharides also plays a pivotal role in the extent of bioavailability and the release profile of the entrapped drug. This chapter briefly explains the possible ways polysaccharides are used in the field of drug delivery mainly as antimicrobials.

## Polysaccharides as Antimicrobial Agents

The consistent growth of polysaccharides into different branches of science has been thoroughly established due to their unique properties as discussed in the introduction. In general, factors like biodegradability, cytocompatibility, biodistribution, modification of functional groups, and minimal side effects prove the effectiveness of polysaccharides (natural as well as synthetic proficient) in drug delivery [31, 32].

According to the Structural Activity Relationship (SAR), functional groups present in some polysaccharides have an innate antibacterial ability capable of being used in biomedical applications. Khemakhem et al. reported the antibacterial activity of polysaccharides that were extracted from olives [33]. A study conducted by Anitha et al. on leaf extracts of *Citrus grandis* provided strong evidence that the composition of the plant was polysaccharide and had reactive functional groups like amine, amide, aromatic alcohol, alkane, alcohol, esters, phenol, and nitro compounds primarily responsible for its antimicrobial activity. The work led by Sehei et al. clearly pointed out the role of the carboxylic groups in polysaccharides showing antibacterial activity. However, the extent of killing bacteria depended upon the virulent strains and further redecorating the group to strengthen antibacterial activity. The study also detailed out the modification of carboxylic groups into amides and esters to increase antibacterial activity [34]. Therefore, in short, the major functional groups responsible for antimicrobial activity are C-O, C=C, -C-H, N-O, C-H, O-H, N-H, =C-H, and C=O [35]. Tuning the activity of functional groups may result in much more potential antimicrobial activity. Amongst all natural polysaccharides, chitosan has an inherent broad-spectrum antimicrobial activity and, thus, it has also been widely used as an antimicrobial delivery vehicle.

## Polysaccharide-Based Antimicrobial Delivery Vehicles

Table 2 summarizes the key findings of each polysaccharide-based antimicrobial drug delivery vehicles.

**Table 2** Key findings of polysaccharides

Polysaccharides	Type	Antimicrobial delivery vehicles	Most targeted bacteria	Key findings
Chitosan	Cationic polysaccharide	Nanoparticle Microparticle Coatings Films Sponges Hydrogels	<i>Staphylococcus epidermidis</i> , <i>Staphylococcus aureus</i> , <i>Salmonella</i> sp.	Inherent antibacterial property. Inhibits Gram-positive bacteria selectively inhibiting <i>Staphylococcus aureus</i> via inhibiting RNA and protein synthesis
Alginate	Hydrophilic linear polysaccharide	Sponges Hydrogels Nanofibers Nanoparticle Microparticle Beads	<i>Staphylococcus aureus</i> , <i>Micrococcus</i> , <i>Escherichia coli</i> , <i>Bacillus subtilis</i> , <i>Propionibacterium acne</i> , <i>Escherichia faecalis</i> , <i>Escherichia cloaceae</i>	Excellent antibacterial carrier and drug delivery vehicle. Strong gelling property helps in achieving uniform bonding with antibacterial molecules

(continued)

**Table 2** (continued)

Polysaccharides	Type	Antimicrobial delivery vehicles	Most targeted bacteria	Key findings
Carrageenan	High molecular weight polysaccharide	Nanoparticle Microparticle	<i>Staphylococcus aureus</i> <i>Bacillus cereus</i> <i>Escherichia coli</i> <i>strains</i>	Available in three fractions. Among which Kappa carrageenan is widely used as antimicrobial drug delivery vehicle due to its ideal properties in combining with antimicrobial formulations
Pectin	Highly branched polysaccharide	Nanoparticle Microparticle	<i>Escherichia coli</i> , <i>Staphylococcus epidermidis</i> , <i>Helicobacter pylori</i>	Pectin is easily amenable to form three-dimensional network in enhancing antibacterial activity with other carrier molecules
Dextran	Complex polysaccharide of glucan	Nanoparticle Microparticle Hydrogel	<i>Staphylococcus aureus</i> , <i>Bacillus cereus</i> , <i>Listeria monocytogene</i> , <i>Bacillus luteus</i> , <i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i> <i>Escherichia coli</i>	Dextran serves to be a good organic carrier matrix in combination with organic and inorganic materials
Guar gum	Hydrocolloid	Nanoparticle Microparticle Hydrogel	<i>Staphylococcus aureus</i> <i>Escherichia coli</i>	Gel formation property with minimal toxicity makes guar gum suitable to get mixed with antimicrobial compounds
Hyaluronic acid	Non-sulfated glycosamino glycan	Nanoparticle Microparticle Hydrogel Scaffold	<i>Staphylococcus epidermidis</i> , <i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i>	No direct influence in inhibiting bacteria. But provokes responses for promoting wound healing and helps in reducing prolonged inflammation cascade and matrix stabilization
Cellulose	Linear polysaccharide	Nanoparticle Microparticle Hydrogel	<i>Staphylococcus aureus</i> <i>Escherichia coli</i> <i>Salmonella choleraesuis</i>	Widely distributed polysaccharide. Applications of cellulose are never limited for antimicrobial carrier, since it also serves as an excellent molecule in enhancing bone responses and mineralization



## ***Chitosan***

Chitosan is a naturally occurring polysaccharide obtained by the alkaline deacetylation of chitin, which is present in the exoskeleton of insects, crustaceans, and fungal cell walls. Chitosan is regarded as the second most abundant polysaccharide present after cellulose. It is a copolymer of 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-N-acetyl-D-glucopyranose units linked via a  $\beta$ -1,4-linkage. Chitosan is not soluble in neutral or alkaline pH and hence is strictly insoluble in water. However, in acidic conditions ( $\text{pH} < 6$ ), free amino groups present in the chitosan molecules get protonated to dissolve chitosan. The solubility of chitosan depends upon N-acetyl groups and distribution of the free amino groups present [36]. The polymer is completely soluble in dilute acids like acetic acid, malic acid, lactic acid, and formic acid [37]. Generally, the viscosity of chitosan increases with increases in chitosan concentration. Owing to its polycationic nature, chitosan is very active and can easily react with an anionic polysaccharide, proteins, fatty acids, and phospholipids. For many years, chitosan has been extensively used as a biomaterial for various applications in the biomedical field due to its unique properties like biocompatibility and biodegradability. It has also exhibited excellent hemostasis and tissue regeneration properties to find use as a wound dressing material. HemCon<sup>TM</sup>, Axiostat<sup>®</sup>, Tegaderm<sup>®</sup>, etc. are chitosan-based wound dressings, are the FDA approved, and are commercially available in the market [38].

Chitosan has been extensively used as a drug delivery carrier and numerous articles have been published since the 1990s on its use highlighting that interest is still high in chitosan as a biomaterial [39]. The main merits of this polysaccharide are properties like (a) non-toxicity, (b) cost-effectiveness, (c) organic solvents not required for solubilization, (d) polycationic nature for ease of chemical tailoring and, finally, (e) carrier matrix ability for delivery systems such as films, sponges, hydrogels, etc. Chitosan has limited applications for the delivery of hydrophobic drugs as a result of its insoluble nature in organic solvents, which gave rise to various derivatives of chitosan [40]. Drugs can be directly mixed into viscous solutions of chitosan or can be conjugated via a hydrolyzable bond to a chitosan backbone and further formulated into different delivery vehicles [41]. Chitosan binds easily to proteins, DNA, and RNA that can be useful for the prevention and treatment of infections using vaccines or gene therapy.

## **Chitosan Nanoparticles**

Chitosan nanoparticles (CNPs) demonstrate better antibacterial potential than chitosan, which is attributed to the polycationic nature of CNPs having a greater surface area to interact with bacterial cell walls compared to pure chitosan [42]. In the previous report, CNPs loaded with different antibiotics have been developed as a delivery carrier. Results demonstrated that the antibiotic-loaded CNPs inhibit and destroy the growth of both Gram-positive and Gram-negative bacteria [43]. A study performed by Madureira et al. found that the bare CNPs prepared by an ionic gelation method possessed antimicrobial activity [44].

Elbi et al. developed fucoidan-coated ciprofloxacin-loaded CNPs for the treatment of intracellular and biofilm infections of *Salmonella*. It was observed that the fucoidan-coated CNPs exhibited anti-*Salmonella* activity twofolds higher than CNPs and sixfolds higher than ciprofloxacin alone [45]. Piras et al. developed antimicrobial peptide temporin B loaded CNPs for long-term antibacterial activity against clinical isolates of *Staphylococcus epidermidis* [46]. Recently, CNPs have been explored as effective inhibitors of multidrug-resistant skin microorganisms with an average minimum inhibitory concentration (MIC) of 1.5 mg/mL [47]. It was observed that the integration of lysozymes into the CNPs improved antibacterial performance possibly due to the ability of nanoparticles to penetrate the cell membrane, enzyme activities and interference with bacterial metabolism [48].

### Chitosan Microparticles

Chitosan microparticles prepared by an ionic crosslinking method employ strong antibacterial activity against various microorganisms via binding to the bacteria outer membrane protein A and lipopolysaccharide [49]. Chitosan microparticles exerted broad-spectrum antimicrobial activity against antibiotic-resistant microorganisms [50]. Jeon et al. reported the application of chitosan microparticles for the treatment of metritis and provided promising evidence for the use of chitosan microparticles as an antimicrobial agent for controlling the growth of pathogens [51]. Shen et al. developed carboxylated chitosan/silver hydroxyapatite hybrid microparticles prepared via a simple gas diffusion method. Excellent antimicrobial activity of hybrid microspheres against *Staphylococcus aureus* could be attributed to the synergistic effect of silver ions and carboxylate chitosan [52]. Cefepime loaded O-carboxymethyl chitosan microspheres with sustained bactericidal activity and enhanced biocompatibility was previously reported [53]. The dual delivery of growth factors and antibiotics from chitosan microparticles was reported for antibacterial activity against *Staphylococcus aureus* and promoting osteoblast proliferation. Significant antibacterial activity was observed along with remarkable proliferation of osteoblasts in the presence of cefazolin (50–100 µg/mL) and BMP 7 as compared to BMP 7 alone, which indicated that the cefazolin might play a role in the proliferation of osteoblasts [54]. Curcumin-conjugated chitosan microparticles showed good anti-inflammatory, antioxidant, and antibacterial activity [55]. Chitosan–alginate microspheres prepared by Ca<sup>2+</sup> ionic crosslinking method demonstrated greater antibacterial and antibiofilm activity against multidrug-resistant microbial pathogens [56].

### Chitosan Coatings

A viscous solution of chitosan was obtained by dissolving chitosan in an acidic solution. Using ionic or polyelectrolyte complexes can enhance the bioadhesive property of chitosan. Due to the polycationic nature of chitosan, it can readily react

with negatively charged mucins, which are present on/in mucosal tissues. Thus, a drug-loaded chitosan solution or chitosan-coated implant enhances the *in vivo* residence time in the target tissues and ultimately helps to increase bioavailability. Abdelbary et al. prepared chitosan-coated liposomes loaded with ciprofloxacin hydrochloride via a thin film hydration method for ocular delivery. Mucoadhesive chitosan-coated liposomes demonstrated improved antibiotic retention, *in vitro/in vivo* antibiotic elution and physicochemical stability [57]. Norowski et al. proved the efficacy of tetracycline-loaded chitosan-coated titanium implants against pathogenic bacteria responsible for implant-associated infections for almost 7 days. Additionally, coated implants demonstrated a slight inflammatory response similar to uncoated implants, when tested using a rodent muscle pouch model. However, the coated implant did not exhibit any cytotoxic effects on human fibroblasts and osteoblast cells [58].

### Chitosan Films

Chitosan films have also provided to be a good platform for drug delivery because they can be easily applied over the surgical sites or wound surface due to its flexible nature. Noel et al. demonstrated that amikacin- and daptomycin-loaded chitosan films have shown excellent antibacterial activity against *Staphylococcus aureus* for almost 72 h [59]. Further, Smith et al. evaluated the ability of daptomycin/vancomycin-loaded chitosan films prepared using chitosan with 61, 71, and 80% degree of deacetylation (DDA) to prevent or lessen musculoskeletal fixation device-related infections. The results indicated that the chitosan films with 80% DDA had a great potential to prevent *Staphylococcus aureus*-mediated musculoskeletal infections [60].

### Chitosan Sponges

Chitosan sponges possess an excellent ability to provide a higher release of antibiotics above the MIC for a longer period of time and increased loading efficiency owing to their porous network. Chitosan sponges can be easily loaded with antibiotic drugs simply by dissolving them in a chitosan solution. Previously, antibiotic-loaded chitosan sponges have been employed as a sustained release system for wound healing in dental surgery [61]. Gentamycin containing chitosan bars have been developed for the treatment of bone infections [62]. Noel et al. investigated the drug releasing chitosan sponge for the prevention of orthopedic and musculoskeletal infections. Chitosan sponges prepared by lyophilization were dipped into a 10 mL of an antibiotic solution containing 5 mg/mL of vancomycin and amikacin each. The release of vancomycin (40 µg/mL) and amikacin (13 µg/mL) showed that these sponges have potential clinical applications for the prevention of early-stage infections in small surgeries [63]. Chitosan acetate sponges commercialized as HemCon™ burn dressings incorporated with silver

nanoparticles (AgNPs) [64] and a bilayer chitosan wound dressing loaded with silver sulfadiazine [65] showed synergistic bacterial inhibition activity in burns and wound infections. *Phaeochamud* and *Charoenteeraboon* developed doxycycline-loaded glutaraldehyde cross-linked/non-cross-linked chitosan sponges and evaluated their antibacterial activity [66]. They observed that the non-cross-linked sponges showed a slower release of drugs as compared to cross-linked sponges because the former could form a gel network, which might have prevented drug diffusion. Pawar et al. developed cefuroxime- and ciprofloxacin-loaded chitosan sponges for the prophylaxis and treatment of orthopedic implant-associated infections. Results showed that the cefuroxime and ciprofloxacin chitosan sponges provided sustainable antibacterial activity against *Staphylococcus aureus* for 25 and 13 days, respectively [67].

### **Chitosan Hydrogels**

Hydrogels are physical or chemical cross-linked polymer networks that contain high hydrophilic groups or domains. Hydrogels can be formulated into different shapes and sizes so that they can be easily applied into any irregular shape wounds and defects. The release of drugs from the hydrogel matrix as a function of time is categorized as swelling-controlled, diffusion-controlled, and chemically controlled mechanisms. However, the primary mechanism for regulating therapeutic drug release is the diffusion of the drug from the hydrogel matrix [68]. Injectability, rapid clearance, and degradation behavior of chitosan hydrogels makes them an excellent local delivery carrier for various biomedical applications [69]. Wu et al. have developed a gentamycin-loaded chitosan/carboxy methylcellulose (CMC) hydrogel cross-linked with genipin. It was observed that genipin concentrations played an important role in the release profile and provided adequate antibacterial efficacy with good osteoblastic cell responses [70]. In the previous report published by Chen et al., the hydrogel was formed by mixing chitosan and hydroxyl propyl methyl cellulose (HPMC) for the targeted delivery of photodynamic inactivator toluidine blue into *Staphylococcus aureus* biofilms [71]. A composite complex containing chitosan, CMC, and magnetic iron oxide showed the controlled release of different antibiotics with minimum cell toxicity [72].

### ***Alginate***

Alginate is a hydrophilic linear polysaccharide, which is widely used in the biomedical field for various applications. Alginate is a salt of alginic acid commonly seen in brown algae. Alginate is produced on a large scale by two methods, the alginic acid method and calcium alginate method. The presence of phycocolloids in the thalus serves as the integral material in providing strength and resilience to the algal component. This causes the accumulation of divalent ions aiding in gel

formation [73]. Properties like solubility, degradability, stability and sterilization, and biological parameters like immunogenicity, compatibility, and non-toxicity has allowed alginate to find uses in numerous biomedical applications [74]. It has strong gelling properties in the presence of  $\text{Ca}^{2+}$  ions, thus, widely being used in drug delivery and controlled release applications. Alginate-based antibacterial formulations and studies that have been conducted are discussed below.

### **Alginate Sponges/Hydrogels**

Alginate dressings constitute cellulose fibers obtained from seaweed. An ideal wound dressing material should have high absorbance with minimum adhesion and be nonadherent [75]. It should also be readily available with hydrophilicity properties, causing no hypersensitive reactions. Alginate has the aforementioned properties and is widely used as a wound dressing materials [76, 77]. Moreover, alginate being bacteriostatic, nonallergenic, hemostatic, hydrophilic, highly absorbable, and biocompatible contributes significantly to biomaterials used as dressings to resist bacterial infections [78]. The ability to absorb liquid exudates and transform them into viscous gum makes alginate an appropriate candidate to be used in wound dressings and as an immobilizing vehicle for drug delivery, improving antibacterial properties. Research has unequivocally proven that alginate-based formulations help reduce the wound bed bioburden by reducing microbial invasion [79]. A review article by Stephan et al. elucidated that the combination of alginate–silver was clinically relevant from older times and was effective for the treatment of “at risk” wound infections. The author explained that once a lesion was created on the skin surface, the microbes could easily gain entry and remain in a quiescent stage and upon sensing a favorable environment, they could start to multiply and cause life intimidating sepsis, paving the way to fatalities. Therefore, a combination of alginate–silver on the skin impeded the indocile behavior of microorganisms and destroyed them from causing infections and associated complications [80]. The review performed in the year 2018 by Deborah et al. demonstrated that the alginate-based hydrogels meant for wound applications could hinder bacterial colony formation and enhance faster healing [81]. A general comparison study conducted by Weigand et al. using alginate wound dressing, pure alginate, and alginate containing silver revealed the improved binding of pure alginate to elastase, minimizing free radical production and pro-inflammatory cytokines. The results also suggested that alginate was useful as a basic wound dressing material in the management of exudating wounds capable of hindering microbial growth and in being clinically relevant [82].

### **Alginate Nanofibers**

A recent study conducted by Rafiq et al. developed nanofibers containing sodium alginate-poly(vinyl alcohol) (SA-PVA) and encapsulated essential oils via electro spinning for desirable antibacterial properties [83]. The main intention of the study

was to replace antibiotics with essential oils (cinnamon, clove, and lavender: 0.5, 1, 1.5 %). Essential oils are known to possess excellent antibacterial properties, where limitations are faced in its validation. As the study proved, cinnamon oil was the best combination with SA-PVA nanofibers for antibacterial applications. A study performed by Kokkarachedu et al. reported that the synthesis of nano zinc oxide alginate antibacterial cellulose fibers had the potential to destroy *Escherichia coli*. The study revealed that sodium alginate was an excellent carrier for biomedical applications, and also the findings stated that there was a significant influence on varying the concentration of sodium alginate during fiber synthesis on inhibiting bacteria multiplication [84].

### Alginate Micro/Nanoparticles

Alginate is the most commonly used polymer for preparing microparticles. Alginate nanoparticles are not common due to the formation of aggregates or difficulty in tailoring them to the nano level [85]. Alginate is combined with silver or chitosan to serve as antibacterial nanoparticles [86]. A study conducted by Trandafilovic et al. described the use of alginate for providing a controlled platform for synthesizing zinc oxide nanoparticles (ZnO NP) against *Escherichia coli* and *Staphylococcus aureus*. The authors substantiated the importance of alginate in the field of drug delivery, tissue engineering, and other biomedical applications as a carrier by narrating properties like an affinity toward divalent metal ions and the reaction of alginate toward metals [87]. The study conducted in 2016 developed a sodium alginate stabilized silver/mesoporous silica nanocomposite system to destroy Gram-positive and Gram-negative bacteria. Here, the author implemented a green way for nanocomposite preparation. Mesoporous silica was capped onto AgNPs. Sodium alginate was used in the study to stabilize and enhance the biocompatibility of the composite system [88]. The author Adam et al. developed chitosan–alginate nanoparticles against the treatment of bacteria *Propionibacterium acnes*. After benzoyl peroxide encapsulation in the chitosan–alginate nanoparticles, *Propionibacterium acnes* was inhibited and the nanoparticles exhibited anti-inflammatory property causing reduced toxic effects to eukaryotic cells [89]. A study conducted by Jianhua et al. described the synthesis of  $\epsilon$ -polylysine encapsulated chitosan–alginate nanoparticles for antibacterial activity. The formulation demonstrated enhanced inhibition of bacteria when tested against *Staphylococcus aureus*, *Micrococcus*, *Escherichia coli*, and *Bacillus subtilis*. Alginate in the formulation extensively absorbed moisture from the environment and proved to serve as a barrier for bacterial entry. Interestingly, the study concluded that  $\epsilon$ -polylysine nanoparticles resulted in a threefold bacterial inhibition over the free drug [90]. The study conducted by Joana et al. included ocular delivery of daptomycin-utilized chitosan-coated alginate nanoparticles. The study was conducted to inhibit methicillin-resistant *Staphylococcus aureus* (MRSA). The formulation was prepared by an ionotropic pre-gelation method in alginate followed by polyelectrolyte chitosan complex formation reactions. The formulation was effective in treating endophthalmitis where the alginate core provided a moist ocular bed and the antibiotic was powerful in destroying the bacteria [91].

## Alginate Beads

In recent studies, it was seen that alginate beads served as an inert nonallergic carrier for tetracycline delivery. The studies promise the use of alginate beads in biomedical applications due to its enhanced compatibility and human compliance [92]. Here, the author developed alginate beads by dropping calcium chloride and immobilizing tetracycline into the beads for sustained antibacterial activity. The results provided evidence of the active disintegration of Gram-positive and Gram-negative bacteria by inhibiting their protein synthesis. Therefore, the authors suggested future prospects for beads to be used in open wounds, hospital room premises, and surgical drapes for enhanced patient compliance. In another study conducted by Selda et al. amoxicillin was covalently immobilized to alginate. The results proved that the amoxicillin-immobilized alginate actively inhibited cell wall synthesis in *Staphylococcus aureus* and *Escherichia coli* species [93]. Another study conducted by Hebeish et al. emphasized surface modification using nanocomposite coatings incorporated with silver composites, and proved that alginate had minimal toxicity and could be an excellent carrier for sustained drug delivery avoiding dosing frequency, whereas silver actively disintegrated and killed bacteria to a great extent [94]. The recent study reported by Deepathomas et al. employed zinc/alginate beads as a carrier matrix for the controlled delivery of rifampicin and it was found that encapsulation efficiency improved as the polymer quantity for bead preparation improved, and the beads exhibited good antibacterial properties with good compatibility toward eukaryotic cells [95].

## Alginate Composite Gel System

Alginate has found uses in tissue engineering hydrogels exhibiting antibacterial properties owing to its smooth and moist bed properties improving cell loading efficiency [96]. A study conducted for *anti-staphylococcal* activity in 2017 revealed the use of alginate as an immobilizing matrix as it promoted quicker wound re-epithelization and helped absorbing wound exudates and preventing cross infection [97]. The authors prepared sodium alginate-polyvinyl alcohol (SA-PVA) hydrogels encapsulating vancomycin coated with polyelectrolytes and vitamin C. The formulation was found to exhibit extended antibiotic release over time, and effectively disrupted *Staphylococcus aureus*. The study was performed in 2010 for assessing the in vitro antibacterial efficacy of sodium alginate and Na-CMC as a carrier hydrogel matrix for gatifloxacin. The study proved that, with an increase in sodium alginate concentration, more encapsulation and greater antibacterial effects were seen against *Staphylococcus aureus* and *Escherichia coli*. The alginate used in the study was used to enhance the mucoadhesive force, and the antibiotic effectively reduced the total bacterial count [98]. In our lab, we developed CNPs and povidone iodine loaded in situ alginate composite hydrogels for prophylaxis and the treatment of orthopedic implant-associated infections, which was found to be a promising candidate for preclinical and clinical applications [28]. A study conducted by Shilpa et al. developed AgNPs through an ecofriendly approach involving sodium alginate and chitosan composite films.

The author described the use of natural polymer alginates to serve as a stabilizer and reducing agent for metallic nanoparticles and their suitability for antibacterial applications [99].

## ***Carrageenan***

Carrageenans are high molecular weight polysaccharides, which have found immense applications in the biomedicine and food industry [100]. Carrageenan is mainly available in three fractions out of which kappa carrageenan is widely used in antimicrobial studies due to its cytocompatibility, degradability, mechanical strength, hydrophilicity, and gelling properties. Another study conducted by Swarup et al. prepared carrageenan-based ZnO NP for improved antibacterial properties. The results confirmed that the combination of carrageenan/ZnO NP showed a good antibacterial effect with ample thermal stability, good mechanical strength, and water vapor barrier properties [101]. A study conducted by Shojaee et al. confirmed the antibacterial film forming ability of kappa carrageenan incorporated with zataria multiflora bois (ZEO) and metha pulegium (MEO) essential oil [102]. Though both essential oils have the capacity to destroy bacteria, ZEO-incorporated carrageenan films were found to be more potent antibacterial films. The formulation was found to disrupt *Staphylococcus aureus* followed by *Bacillus cereus* and later *Escherichia coli* strains. A study conducted by Annabella et al. revealed the optimal elasticity, smooth morphology to absorb exudates, adhesiveness, and excellent mechanical strength of carrageenan. Multilayer assemblies of polyethyleneimine and carrageenan exhibited a synergistic effect against pathogenic bacteria. The results exhibited contact killing of *Staphylococcus aureus*, *Escherichia cloacae*, and *Escherichia faecalis* [103]. A study conducted by Fawal et al. also proved the contact killing effect of bacteria. Carrageenan films were plasticized with glycerol and encapsulated with citric acid. Upon contact with citric acid, more bacteria died. The reason might be due to the unfavorable acidic content. The results proved the inhibition of *Staphylococcus aureus*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Dickeya chrysanthami* strains indicating the antibacterial potency of the formulation [104].

## ***Pectin***

Pectin is a natural polysaccharide obtained from various fruit extracts using enzymatic or catalytic methods. Pectins are widely present as a constituent of the cell wall of many plants. Pectin is a highly branched polysaccharide macromolecule, consisting of at least three domains: (a) Homogalactoronan, (b) Rhamnogalactoronun I, and (c) Rhamnogalactoronun II. Homogalactoronan is the major component of the pectin polysaccharide, which is basically composed of chains of D-galacturonic acid units linked by  $\alpha$  (1-4) glycosidic linkages that can be methyl esterified (some extent <10%) and in some cases partially acetyl esterified. A highly concentrated



solution of pectin can be easily formulated into a flexible, three-dimensional hydrogel network, which is widely used for biomedical applications. A water-insoluble pectin gel could be obtained by using divalent or trivalent cations that can swell in an aqueous medium but do not dissolve.

Ciprofloxacin hydrochloride-loaded pectin microspheres have been developed for the treatment of osteomyelitis. The microspheres were prepared using the spray drying method, which exhibited a release of ciprofloxacin for 48 h. In vivo results demonstrated that the biodegradable pectin microspheres were able to maintain aseptic conditions at the site without impeding new bone formation [105]. Pallavicini et al. prepared AgNPs with pectin (P-AgNPs) wherein pectin acted as a reductant and coating agent. It was observed that P-AgNPs demonstrated excellent antibacterial and antibiofilm action at a lower  $\text{Ag}^+$  ion release rate against *Escherichia coli* and *Staphylococcus epidermidis*, as compared to ionic silver. In addition, P-AgNPs were able to promote fibroblast proliferation and, thus, it could be a potential medication for wound healing as well as for effective prophylaxis of implant-associated surgical site infections [106]. In a previous report published by Martinez et al., pectin-polyvinyl alcohol (P-PVA) cryogel patches were developed as a controlled release system for enrofloxacin and keratinase enzyme for antimicrobial treatment in wounds and scars. In this report, pectin with a different degree of esterification (71%, 62%, 55%, and 33%) and three concentrations (0.50%, 0.75% and 1% w/v) were tested to optimize enrofloxacin and keratinase release. Results suggested that the PVA cryogel containing pectin at a 0.50% w/v concentration and 55% degree of esterification exhibited the highest release of keratinase [107]. Finally, it was observed that the controlled release of enrofloxacin and keratinase could be modified by tailoring the amount and concentration of pectin with different degrees of acetylation in the PVA cryogel patches developed for antimicrobial treatment. The levofloxacin-loaded silver phosphate ( $\text{Ag}_3\text{PO}_4$ )-pectin microspheres could be used as an effective antimicrobial agent for medical applications against *Escherichia coli* and *Staphylococcus aureus* [108]. Silva et al. developed amoxicillin-loaded covalent  $\text{TiO}_2$ -co-pectin microspheres containing  $\text{Fe}_3\text{O}_4$  nanoparticles for the treatment of *Helicobacter pylori* associated ulcers. The nanostructured pectin microspheres showed great pharmacological potential [109]. In one of the previous report, a novel bioactive zinc cross-linked pectin–sodium alginate based film was prepared for antimicrobial activity particularly for disinfection of medical devices [110]. Therefore, it could be concluded that the biopolymer pectin played a significant role as an active antibacterial carrier molecule in vivid formulations for hindering and destroying bacteria colonization.

## **Dextran**

Dextran is a complex glucan synthesized via polymerization of  $\alpha$ -D-glucopyranosyl of sucrose catalyzed by the dextranase enzyme. Dextran generally shows a negative effect on thrombocyte aggregation and coagulation factors [111]. Therefore, dextran is commonly used as an adjuvant and not used in higher concentrations for

formulations. Though dextran does not have any direct influence on antibacterial and osteoinductive properties, it serves as an excellent carrier matrix in combination with other organic and inorganic materials [112]. Research conducted by Yang et al. revealed the use of dextran as a capping agent in the preparation of antibacterial AgNPs. Results confirmed the equal distribution of the size and shape of AgNPs due to dextran capping. The formed nanoparticles were highly potent and destroyed Gram-positive and Gram-negative bacteria (*Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*), with minimal toxic reactions when tested on mouse fibrosarcoma cells [113]. Studies also reported the use of dextran as an immobilizing matrix hydrogel for enhancing antibacterial activity. The study performed by Jiaul et al. synthesized formulations to destroy biofilms, which are the reason for the most debilitating disorders. The study performed utilized biocides incorporated with dextran methacrylate hydrogels. The results suggested that the direct loading of a biocide in the hydrogel formulation had >99.99% annihilating effect on *Staphylococcus aureus*, *Escherichia coli*, and MRSA biofilm formation. The study suggested the formulation as a potential candidate especially for topical infections [114].

Felicetta et al. developed a dextran hydrogel loaded with gentamicin. The result showed that the high antibacterial efficacy lasted, up to 24 days maintained the ideal hydrogel properties, and was capable of disrupting the already formed bacterial biofilm. The result also proved that the formulation was more potent than the pure gentamicin sulfate [115]. The study performed by Hogue et al. was for the development of a dextran methacrylate hydrogel with biocide loading to destroy biofilm formation. Apart from biofilms, the formulation was 100% efficacious to MRSA, and its activity was maintained for up to 5 days. Besides antibacterial applications dextran-based hydrogels also proved suitability for use in enhanced cellular growth, differentiation, and proliferation [116]. A study conducted by Nina et al. illustrated the application of dextran in wound dressings and skin tissue engineering applications. The nanofibers were synthesized using an electrospinning technique involving three polymers: polycaprolactone, cellulose acetate, and dextran incorporating tetracycline hydrochloride into the fibers. The author highlighted that the prepared fibers improved adhesion and proliferation of cells and exhibited sustained antibacterial drug release with good antimicrobial activity against Gram-positive and Gram-negative bacteria [117]. Another interesting study conducted by Maggie et al. described the use of dextran aldehyde in the form of a hydrogel in preventing bacterial adhesion and further limiting their growth after surgical procedures. The study aimed to compare antibacterial activity, biocompatibility and wound healing capacity of the hydrogel. The findings of the study concluded that the wound closure after a period of 72 h upon the application of the formulation had ample biocompatibility and good antibacterial properties [118].

Author Milorad et al. have developed AgNPs stabilized with dextran sulfate involving a chemical reduction green synthetic method. The approach was put forth to utilize nontoxic, biodegradable polysaccharides for the reduction and stabilization of the prepared nanoparticles. The results obtained for the study were extremely convincing in that the dextran sulfate stabilized AgNPs exhibited strong antibacterial properties against *Staphylococcus aureus*, *Bacillus cereus*, *Listeria monocytogenes*,

*Bacillus luteus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli* [119]. A study conducted by Afeesh et al. reported the synthesis of scaffolds using polyurethane and dextran incorporated with ciprofloxacin. The results illustrated that the antibacterial drug ciprofloxacin was released in a controlled manner with the aid of dextran as a nanocarrier, where the cells were unaffected, and the scaffold possessed good bacterial inhibition properties [120].

## **Guar gum**

Guar gum is a hydrocolloid, which has tremendous applications in medical science. The ability to form a thick paste without gel formation makes it unique for antibacterial applications with improved patient compliance [121]. A study conducted by Balbir et al. prepared guar gum/polyaniline/polyacrylic acid based interpenetrating hydrogels by a two-step polymerization process. The resulting gel was confirmed to be electrically conductive with antibacterial properties [122]. The study conducted by Reema et al. proved the antibacterial applications of guar gum in combination with acrylic acid incorporated polyaniline. The results confirmed the antibacterial properties of the hydrogel on *Staphylococcus* and *Escherichia coli* species [123]. A study conducted by Runa et al. modified guar gum intrinsically to a novel biopolymer for wound healing applications thereby obstructing bacterial entry. This evidence proved the promotion of wound closure with no trace of antibacterial entry. Further, it induced the proliferation and migration of cells at the scar tissue [124].

## **Hyaluronic Acid (HA)**

Hyaluronic acid (HA) is a biopolysaccharide belonging to the class of non-sulfated glycosaminoglycans, with constant disaccharide seen mainly in connective and epithelial tissues [125]. HA is non-immunogenic, cytocompatible, biodegradable, angiogenic, and osteoconductive [126]. HA plays a pivotal role in the wound healing cascade [127]. HA enhances inflammation essential for promoting wound healing and later minimizes long-term inflammation and aids in stabilization of the matrix and therefore is regarded as a good carrier for antibacterial applications [128]. Though HA does not contribute directly to biocidal activity, it serves as an excellent carrier matrix for antibacterial activity [129]. One such study performed by Leyre et al. elucidated the development of layer-by-layer assembly of HA with chitosan onto poly(ethylene terephthalate). The findings concluded that the coating resulted in inhibiting bacterial adhesion. The selective layer approach enabled the long-term release of antibacterial components making it suitable for implementing in implant substrates [130]. The study reported by Andrea et al. explained in detail the influence of HA in annihilating bacteria. The study conducted on 15 ATCC strains revealed that HA was found to exhibit dose-dependent growth inhibition of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus mutans*,

*Candida glabrata*, *Candida parapsilosis*, and *Enterococci* [131]. The fast resorbable HA-based hydrogel when tested preclinically and clinically was found to be effective and safe for intraoperative use and can be easily spread onto direct implant sites for bacterial adhesion prevention [132]. A study conducted by Isabelle et al. modified HA to exhibit antibacterial characteristics by grafting with antimicrobial peptide (nisin) and formulating it in the form of hydrogels. The prepared antibacterial hydrogels when tested on *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* revealed antibacterial activity suggesting the effectiveness of the formulation for use as wound dressing materials, contact lenses, cosmetics and for other biomedical formulations [126].

## Cellulose

Cellulose is a linear polysaccharide consisting of repeated glucose subunits and one of the most abundant polysaccharides on earth [133]. The major structural components in plants are made up of cellulose and are very suitable candidates for biomedical applications [134]. Some of the exciting characteristic features include bioavailability, degradability, low density, ease of reproducibility, enhanced chemical persistence, and thermal constancy making it suitable for several other multifarious applications too [135, 136]. Though cellulose has no role in possessing antibacterial activity, a facile approach in producing antimicrobial cellulose components is of much research interest [137, 138]. Considering these aspects, a study conducted by Kamyar et al. was successful and has concluded that cellulose could contribute to the area of drug delivery especially transdermal or wound dressing patches [139]. A study conducted by Afeesh et al. revealed the use of cellulose acetate together with zein and polyurethane for wound dressing applications. The author produced substantiating evidence for the use of a cellulose biopolymer in a study due to its hydrophilicity and good adsorption characteristics, which are considered to be the essential requisites of wound dressing preventing antimicrobial attack [140]. Incorporating a minimal amount of antibiotic streptomycin sulfate to the wound mat improved bactericidal activity with controlled release of the formulation improving patient compliance. Applications of cellulose are never limited for antimicrobial, since it also serves as an excellent molecule in enhancing bone responses and mineralization. A study conducted by Sa Liu et al. reported the importance of cellulose as a carrier material for destroying bacteria. The authors developed a bacterial cellulose/collagen and hydroxypropyltrimethyl ammonium chloride chitosan mesh composite. The finding suggested growth impairment of *Staphylococcus aureus* and *Escherichia coli* proving mesh biocompatibility and antimicrobial ability [141]. A study performed by Susan et al. involved non-covalently combined cellulose to aid as a stabilizer in synthesizing ZnO-silver heterostructure nanoparticles. Antibacterial studies were evaluated using *Salmonella choleraesuis* and *Staphylococcus aureus* exhibited significant inhibition of bacterial growth [142]. A study performed by Mazhar et al. prepared a nanocomposite film of regenerated bacterial cellulose embedding ZnO NP into it. The results showed an

excellent bactericidal effect with reduced toxic reactions upon testing in vitro and favored cell adhesion [143]. A further study developed nanocellulose films consisting of phytogetic nano-bactericides of silver and found that cellulose, when fine-tuned and non-covalently bonded with metallic particles, could effectively target bacteria and the same was proved with the exotic species compendium of activities to protect the ecosystem (ESCAPE) communities who are at the largest risk of threats due the economical crisis.

## Conclusion

Implant materials should be biocompatible, provide a favorable environment for bone tissue regeneration and should have the ability to prevent the adhesion and growth of microorganisms. Despite tremendous advances in the prophylaxis and the treatment of implant-associated infections, it remains a most devastating problem in orthopedics. Various antimicrobial delivery vehicles have been developed to encounter the bacteria present at the implant site. Polysaccharide-based antimicrobial delivery carriers are amongst the most novel approaches employed for the management of implant related infections. They are widely used in the biomedical field for drug delivery applications due to their advantageous properties such as non-toxicity, easy availability, biocompatibility, capability of tailoring their functionalities for improving antimicrobial properties, and biodegradability. They can be fine-tuned via chemical modifications, blending of two or more polymers, surface modification and conjugation with other polymers or the drug itself to develop controlled and sustained release antimicrobial delivery systems. Chitosan has inherent antibacterial activity. Thus, it is a promising candidate amongst polysaccharides for antimicrobial delivery due to potential synergistic activity with other antimicrobial agents. Considering the advantages of polysaccharide-based antimicrobial delivery vehicles, we should dedicate our research to develop a novel commercially available sustained release, effective and nontoxic delivery system for infection prophylaxis. In the next 10 years, we hope that new polysaccharide-based formulations will emerge to eradicate the bacteria present at various implant sites for a prolonged period and reduce chances of infection.

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