Cellulose-Based Antimicrobial Materials

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Abstract Cellulose is a widely studied natural polymer due to its availability, biodegradability, non-toxicity, and ease of chemical modification. Currently, cellulose has many applications in science and technology, but it has vast relevance in biomedical applications, such as a protective coating for wound dressing in skin burns, and injuries to avoid bacterial infections. This chapter describes some properties of cellulose such as structure, and biocompatibility. Besides this chapter also describes some methods used to endow cellulose with antimicrobial activity by means of the addition of biocidal groups as *N*-halamines, quaternary ammonium salts, nanoparticles, enzymes, or through the incorporation of antibiotics for controlled drug delivery.

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1 Introduction

Cellulose has been widely studied as a biomaterial because it is one of the most abundant and biodegradable natural polymers. This possesses remarkable physical and biological properties and an adequate surface chemistry (Zhu et al. 2010; Zhu and Zhuang 2012). Besides, its hydrophilicity, transparency, and innocuousness make it an alternative for various applications, especially to develop materials related to wound dressings and nanomaterials for severe skin burns, injuries, and bacterial infections treatment. Other cellulose applications include tissue engineering, controllable delivery systems, sensors, agriculture, and water and blood purification (Chang and Zhang 2011). For medical treatments, plant-based cellulose has been mainly used as cotton for wound dressing, sutures, and dialysis membranes (Cross et al. 2006). Nevertheless, the plant-based cellulose is not produced in its purest form, lignin, hemicelluloses, and other compounds are part of its composition, and purifying it for medical applications is a highly complex process. The production of bacterial cellulose (BC) is a cleaner alternative; BC is biosynthesized by several bacteria and shares the same chemical structure with plant cellulose, except that it exhibits the highest purity making it suitable for medical device applications. Some bacteria of genera *Acetobacter*, *Rhizobium*, *Agrobacterium*, *Aerobacter*, *Achromobacter*, *Azotobacter*, *Salmonella*, *Escherichia*, and *Sarcina* produce BC (Shoda and Sugano 2005).

BC is well-known for being superior compared to plant cellulose regarding sustainability, biocompatibility, biodegradability, ability to be chemically modified, and surface area. BC is endowed with unique properties such as high water holding capacity, a high degree of polymerization, high mechanical strength, and high crystallinity (Esa et al. 2014). Furthermore, the bacterial production of nanocellulose is the most optimal and efficient industrial method yielding a pure product (Kang et al. 2012). All these features make BC an outstanding material for biomedical applications (Vasconcelos et al. 2017).

The continuous interaction between the human body and pathogens is a constant risk for health because of the possibility of acquiring infections, which are produced by viruses, fungi, and bacteria. However, bacterial infections are the most frequent acute and chronic infections and the major cause of morbidity in the world. Currently, the accelerated increase of untreatable bacterial infections is a disturbing issue and is caused by a rise in antibiotic-resistant bacteria strains (Khatoon et al. 2018). In this area, attention has been placed on nanocellulose to develop biocompatible, non-toxic, non-leachable, and antibacterial materials with prolonged biocidal activity (Tayeb et al. 2018; Tavakolian et al. 2020). Some studies have reported innovative and effective technologies that can enhance microbial inactivation by

incorporating biocidal agents in nontoxic and biocompatible materials to avoid bacterial resistance (Delezuk et al. 2017).

Methodologies used to synthesize cellulose antimicrobial materials include surface modification, loading or incorporation of drugs or inorganic nanomaterials, and blending with antibacterial polymers. Antimicrobial materials may include in their composition some agents such as quaternary ammonium compounds, zwitterions, inorganic nanocomposites, and nanoparticles (NPs), being silver and zinc the most widely used to produce NPs (Chen et al. 2012a, b, 2014; Llorens et al. 2012; Heli et al. 2016). Antimicrobial cellulose-based materials expand the cellulose applicability in medical therapies where it can be used to improve wound dressing, packaging materials, and medical prosthesis or to act as drug carriers.

Wound dressing has an important role in the healing process whether surgical, burns, or accidents. Initially, it was considered as passive protection of the wound, which main functions were to keep the wound dry (adsorbing the exudate) and prevent the bacterial proliferation and the incorporation of external agents. However, this concept has changed significantly, and the bandage is now considered an active component during the healing process and has a great importance for the treatment of chronic wounds. The new designs and materials seek to provide a healing microenvironment appropriate for the growth of new tissue (warm and humid environments) but controlling the development of infections by using antimicrobial materials. In this context, cellulose excellent properties make it an interesting material for this application since even though cellulose does not have antimicrobial activity, in its natural form, it can be easily modified to load medications or copolymerize with antimicrobial substances, which will allow preventing or eradicating a possible wound infection. Furthermore, as it is a material with a high affinity for bioactive substances, it accelerates recovery (Bergstrom et al. 2005).

2 Properties of Cellulose

Cellulose is a straight-chain polysaccharide whose monomeric unit is the D-glucose dimer, consisting of two glucose molecules linked through a β-1-4-glycosidic bond, in which the C1 carbon of a glucose molecule and the C4 of the other are covalently bound to an oxygen atom (Azizi Samir et al. 2005). The glucoside bond is stabilized by the hydrogen bonds between glucose hydroxyl groups and the oxygen in the bond, resulting in the linear configuration of the polymer. The aforementioned microscopic configuration of cellulose allows a more feasible interaction between chains, thus forming microfibrils bonded by Van der Waals forces and intermolecular hydrogen bonds, which promote the assembling of multiple cellulose chains stacking them in a stable and resistant three-dimensional structure. Microfibrils are made up of two structural regions: a crystalline structure, in which the cellulose chains are organized in a very orderly way, and an amorphous region, where the chains are disordered (Nishiyama 2009). The crystalline regions can be extracted from the cellulose microfibrils by acid treatment, resulting in cellulose

nanocrystals (CNC) or nanofibers (CNF) depending on the extraction material. The use of nanotechnology techniques allows the design and manufacture of natural cellulose NPs with different dimensions from 1 to 100 nm, from the fibers by homogenization, hydrolysis, or combined chemical and mechanical processes. Cellulose NPs give versatility and improve the properties of a given material (Vasconcelos et al. 2017).

Crystalline cellulose has four widely studied polymorphs (I, II, III, and IV). The first, cellulose type I, is the most abundant in nature since it is produced by plants, urochordates, algae, and bacteria. This structure can be modified to the other polymorphs (O'Sullvian 1997), through a solubilization-recrystallization processes or by mercerization (aqueous sodium hydroxide treatments). Cellulose II has a monoclinic structure that gives it the greatest stability and has been used to produce various materials including cellophane, rayon, and synthetic textile fibers as the Tencel (Klemm et al. 2005). On the other hand, cellulose III is obtained from cellulose I or II by treatments with liquid ammonia. And finally, cellulose IV is produced by heat treatments of cellulose III (Ishikawa et al. 1997).

Additionally, cellulose I is formed by two coexisting crystalline structures, whose proportion depends on the source of cellulose extraction; a triclinic structure (Iα) and a monoclinic structure (Iβ), which are named depending on their arrangement "parallel upwards" or "antiparallels" (Azizi Samir et al. 2005; Nishiyama 2009). Although the polymorph Iα can be converted into Iβ through hydrothermal treatments (~260 °C) in alkaline solution (Yamamoto and Horii 1993; Watanabe et al. 2006; Horikawa and Sugiyama 2009) or high-temperature treatments in organic solvents and inert atmosphere (Debzi et al. 1991) complete conversion is not achieved.

For example, bacterial cellulose fibrils, when treated, can produce micro or nanofibrils (Costa et al. 2017), without altering their crystallinity, in general, the geometry of the BC is determined by intramolecular and intermolecular forces such as bonds of hydrogen and hydrophobic and Van der Waals interactions, and forms parallel chains (cellulose I). When carrying out the mercerization process (treatment with 5–30 wt% of sodium hydroxide), this material forms a type II antiparallel structure, mostly stabilized by hydrogen bonds, which generates a more stable three-dimensional arrangement than cellulose I and nanofibers with random structure and high Young modulus, 118 GPa for a single BC filament almost comparable to Kevlar® and steel (Picheth et al. 2017). Cellulose micro and nanofibrils have a high surface area, which is related to high porosity and allows greater interaction between the fibrils and decreases the permeability of the material to oxygen. Furthermore, due to a large number of free hydroxyl groups, they show great adsorption of water and the formation of high-viscosity gels. Another advantage of hydroxyl groups is that they can be functionalized by esterification, oxidation, or sulfonation, altering the properties of the biopolymer and expanding the application (Berto and Arantes 2019).

2.1 Biocompatibility

Cellulose is an adequate material for skin engineering materials and medical devices. The toxicity of cellulose has been evaluated through techniques such as cytometric assays, for instance, in an in vivo mice surgeries and in vitro human umbilical vein endothelial cells assays. These assays indicated a nonvisible difference in morphology (Jeong et al. 2010). In another assay, cellulosic composites were implanted into mice and they were successfully integrated into the mice skin. Hence, cellulose cell attachment and proliferation supported that cellulose is non-toxic and biocompatible.

In another study, a synthesis of a composite scaffold by modification of cellulose with poly(3-hydroxubutyrate-co-4-hydroxubutyrate) (P(3HB-co-4HB)) exhibited cell adhesion on Chinese Hamster Lung (CHL) fibroblast cells (Wang et al. 2009). The results indicated better biocompatibility for the BC composite scaffold (P (3HB-co-4HB)/BC) composite scaffold than that for pure P(3HB-co-4HB) scaffold (Zhijiang et al. 2012). On another hand, Lin et al. studied the effectiveness and biocompatibility of cellulose hydrogels as supports for the storage and delivery of extracellular matrices such as collagen, elastin, and hyaluronan, as well as growth factors including the basic fibroblast growth factor (B-FGF), human epidermal growth factor (H-EGF), and keratinocyte growth factor (KGF) (Lin et al. 2011). In vitro cell viability evaluations showed that 95% of the mesenchymal stem cells added to the cellulose support were alive, and could form interactions with collagen, these results showed that cellulose-based materials can promote tissue regeneration and they could be used in skin substitutes (Zhijiang and Guang 2011).

3 Chemical Modification of Cellulose

Cellulose has a large number of hydroxyl groups, which are reactive and act as active sites, allowing a wide variety of chemical modifications that result in unique cellulose derivatives (Jedvert and Heinze 2017).

Chemical modifications provide cellulosic materials with antimicrobial activity by incorporating biocidal agents either by covalent bonds or cellulose binding interactions. The main chemical methods of cellulose modification include esterifications, etherifications, and hydroxyl group oxidation reactions. Other chemical modifications include ionic and radical grafting, acetylation, and deoxyhalogenation (Fig. 1). These chemical modifications may provoke drastic changes in the cellulose solubility allowing water and organic solvents to dissolve it.

Chemical modification of cellulose with different functional groups allows the design of antiadhesive and biocidal materials. Functional groups include siloxanes, silanes, amines, hydrazide, acyl hydrazide, aminooxy, alkenes, alkoxysilanes, acyl chlorides, epoxides, and isocyanates. Although cellulose may require a pretreatment to insert more complex functional groups, the chemical modification is a great alternative for the fabrication of diverse materials at different scales, which is

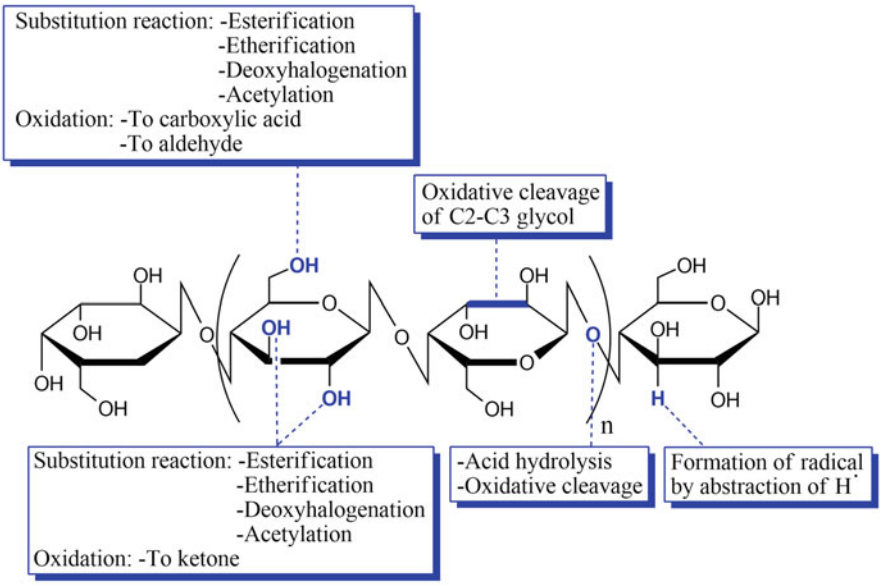

Fig. 1 Chemical reaction on backbone cellulose

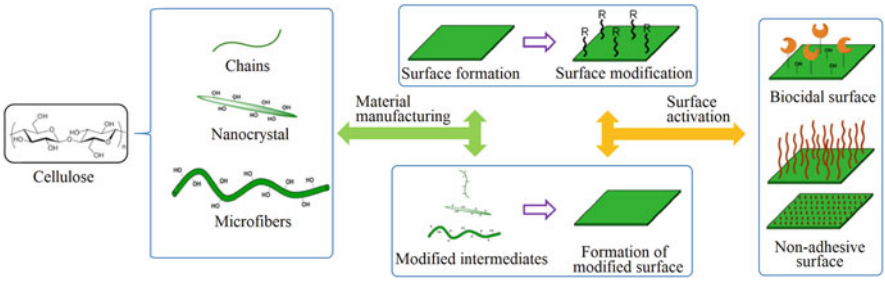

Fig. 2 Chemical modifications are useful to develop cellulose-based antimicrobial materials

achieved by two approaches: from intermediates or semi-finished materials, Fig. 2 shows an overview of the chemical modification process of cellulose.

3.1 Covalent Attachment of Biocide Compounds

Although there are several reports of biocidal agents, *N*-halamines stand out owing to their effective activity against microorganisms such as bacteria, fungi, and viruses. *N*-halamines have in their structure one or more nitrogen-halogen covalent bonds (N-X), which can be formed by halogenation of imides, amides, or amines (Chen et al. 2007). These molecules have generated keen interest due to their stability,

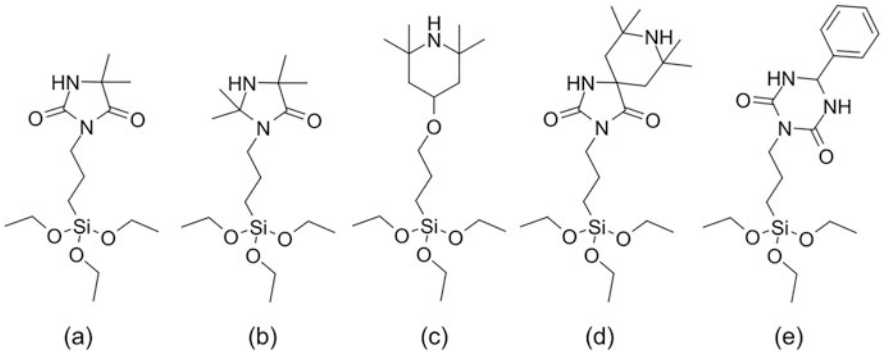

Fig. 3 Chemical structure of *N*-halamines functionalized with siloxanes linkage groups (**a**–**e**) for grafting on cellulose

rechargeability, and non-toxicity (Dart et al. 1991; Sun and Sun 2002; Yuyu and Gang 2002; Kitkulnumchai et al. 2008; Liu and Sun 2008, 2009; Skorb et al. 2008; Jeong et al. 2010; Jiang et al. 2011; Chen et al. 2012a, b). When *N*-halamine precursors are exposed to a sodium hypochlorite solution, chlorinated nitrogenous structures are produced and their antibacterial mechanism is given by oxidative chlorine release. So the interaction between microorganisms and *N*-halamines produces a halogen exchange reaction that causes cell death (Chen et al. 2007). A singular feature of this biocide is that its oxidative chlorine can be regenerated by new exposition to a sodium hypochlorite solution. These characteristics make *N*-halamine an excellent candidate to develop antimicrobial materials from cellulose (Sun and Sun 2003; Liu and Sun 2006, 2009).

In this context, several functional groups have been used to incorporate as *N*-halamine moieties into cellulose, *N*-halamine compounds with siloxane linkage groups (Fig. 3) are one of the most used methods for covalent bond or coating onto cotton fabrics. Siloxane *N*-halamine groups provide to materials antimicrobial activity against Gram-negative and Gram-positive bacteria (Liang et al. 2005, 2007; Barnes et al. 2006, 2007; Liu and Sun 2006, 2008). For example, polymers synthesized through a hydrosilylation reaction with polymetylhydrosiloxane were used to coat cellulose fibers (Chen et al. 2012a, b) and chemical bonding between the siloxane and the cellulose fiber was achieved by copolymerization with siloxane monomer (Kocer et al. 2011a, b), thus providing cellulose with antimicrobial activity against both Gram-negative and Gram-positive bacteria.

Siloxane groups are not the only functional group to graft or form covalent coats with *N*-halamine on cellulose. *N*-halamine with hydroxyl or epoxy group moieties can react with cellulosic materials through the formation of ether bonds, followed by activation using a NaClO solution. However, in these conditions grafting is difficult since the epoxy groups have relatively low activity toward cellulose. Nevertheless there are other alternatives such as the use of vinyl monomers containing amide bonds to induce the graft onto cellulose by free radical polymerization reactions (Liu

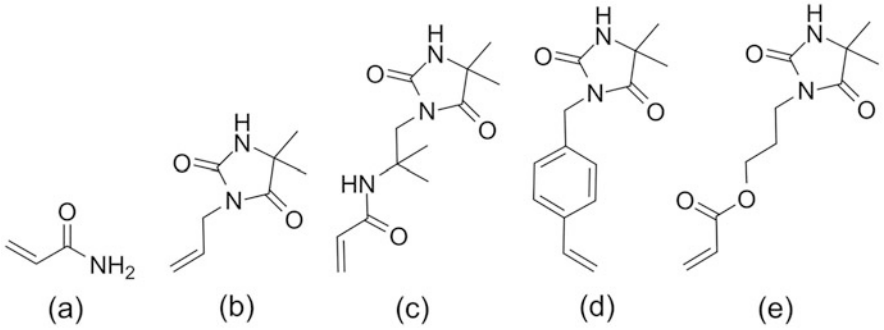

Fig. 4 Chemical structure of *N*-halamines functionalized with vinyl groups (**a**–**e**) for radical grafting on cellulose

and Sun 2006, 2009) or admicellar polymerization, which widen the application range of *N*-halamine compounds (Fig. 4 a–e). For example, the monomer 3--(4′vinylbenzyl)-5,5-dimethylhydantoin (Fig. 4d) was grafted on cellulosic fibers by admicellar polymerization using a cationic surfactant (Ren et al. 2008), the final material exhibited an excellent antibacterial activity (Ren et al. 2009; Cerkez et al. 2011, 2012; Ma et al. 2013).

Another technique used to provide cellulose with *N*-halamines antimicrobial activity is by the layer-by-layer deposition method which is achieved with no covalently bonding groups. In this method, precursors are typically water-soluble, avoiding the use of organic solvents. For instance, poly(2,2,6,6-tetramethyl-4-piperidylmethacrylate-co-trimethyl-2-methacryloxy-ethylammonium chloride) and poly(2,2,6,6- tetramethyl-4-piperidyl methacrylate-co-acrylic acid potassium salt) were used to coat on cellulose fibers by this method (Cerkez et al. 2011).

3.2 Quaternary Ammonium Salts

Nowadays, quaternary ammonium compounds are considered important antibacterial agents since they exhibit antibacterial activity against broad spectrum of bacteria and fungi (Gao and Cranston 2008; Murguía et al. 2008; Massi et al. 2009). The antibacterial activity of quaternary ammonium compounds is mainly attributed to two mechanisms of action: (1) an electrostatic interaction between the cationic charge of the quaternary ammonium with the anionic charge of the cell wall and (2) non-polar interactions and penetration of the quaternary ammonium hydrophobic moiety into the cell wall (CW). These interactions cause the formation of a complex surfactant with the CW, which interrupts the activity of proteins and influences key functions in the cell membrane and even in the bacterial DNA. Another important feature is that the increase in the alkyl chain length improves the antimicrobial activity of the quaternary ammonium compounds; however, if the

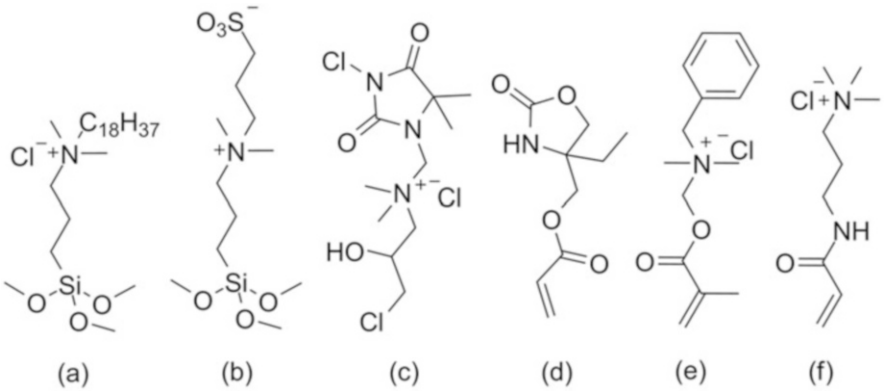

Fig. 5 Cellulose grafts with functionalized ammonium salts, alkoxysilanes (**a**–**b**), alkyl halides (**c**), and vinyls (**d**–**f**)

length is excessive, length may affect the antimicrobial activity due to the formation of micelle-like structures (Tiller et al. 2001; Gilbert and Moore 2005).

Quaternary ammonium compounds have been designed in a similar way to *N*-halamines compounds, groups such as siloxanes and alkoxysilanes are used to covalently bond quaternary ammonium salts to cellulose (Fig. 5). For example, DC-5700 (organosilicon quaternary salt) (Fig. 5a) and sulfopropylbetaine (Fig. 5b) containing reactive alkoxysilane groups were hydrolyzed to form silanol groups (Si-OH), which further reacted with the hydroxyl group (–OH) of cotton fibers and forming covalent bonds (Chen et al. 2011). The toxicological studies on the modified cotton indicated that these quaternary salts cannot be absorbed into the body by contact and the DC-5700 mean lethal dose (LD50) was 12.27 g $kg^{-1} \pm 0.116$ (Li et al. 2012).

3.3 Nanoparticles of Noble Metals and Metal Oxides

The performance of antibacterial NPs depends directly on the particle size and shape. A nanosized structuration renders the capability to translocate in cells and functional organelles, resulting in genotoxicity and cell death. In vitro studies conducted by exposure to NPs have shown that smaller particles and lower concentration can cause greater bactericidal effects (Sudha et al. 2018).

The use of compounds containing noble metals and metal oxide NPs is an adequate alternative for antibacterial materials due to the low corrosion rates and high biocompatibility (Christensen et al. 2010) as well as the correct mechanical properties (Shiraishi et al. 2009). Some metal oxide NPs have been discovered as natural antimicrobials and are incorporated in different nanomaterials, being the most interesting those that contain oxides as CoO, MnO, and Fe_2O_3, which have

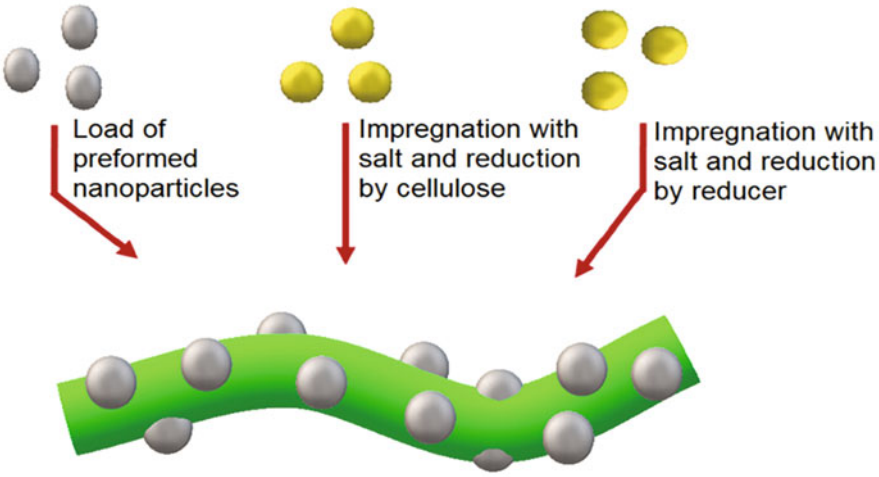

Fig. 6 Methodologies of load NPs on cellulose

shown an excellent antimicrobial activity (Dhineshbabu et al. 2014; Rajendran et al. 2014; Gouda et al. 2015). For example, ZrO_2 NPs is an antimicrobial material that has shown good washing durability and adherence after treatment with microwaves (Gouda and Keshk 2010; Gouda 2012). NPs obtained from metals such as Au, Ag, Pt, and Pd, also known as noble metal NPs, have been extensively investigated due to their unique belongings and applications in science, as they own remarkable biocidal properties when doping in different supports (Fig. 6).

In this context, BC is a common raw material in the production of composites as BC/Ag. Impregnation is a method to provide the BC with biocidal properties for its potential application in skin tissue repair. According to literature, for example, BC is immersed in a silver nitrate solution, followed by in situ metallation using a sodium borohydride solution to reduce the absorbed Ag^+ to Ag(0) NPs. As a result, the obtained BC exhibited strong antimicrobial activity against Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus aureus* (Maneerung et al. 2008).

Even though cellulose is quite stable, new strategies are under development to improve the properties of derivated materials, one of which is the incorporation of NPs in the material. In some cases, the modification of functional groups in cellulose is necessary to get a functional composite with NPs. Covalent and electrostatic binding are strategies to modify the cellulose chains (e.g., siloxane, amines, acyl chloride, and carboxylic acid, among others), the binders must have functional groups available to bind with NPs through electrostatic interactions or covalent bonds. In this regard, Fig. 7 shows the NPs loading in a functionalized cellulose with different chemical groups.

Another strategy to produce antimicrobial cellulose-based materials consists in the coordination of metal centers at the surface. For example, sulfadiazine moieties were used as ligands to obtain a coordination complex with Ag^+; the resulting Ag-sulfadiazine complex was used for the immobilization of antimicrobial cotton

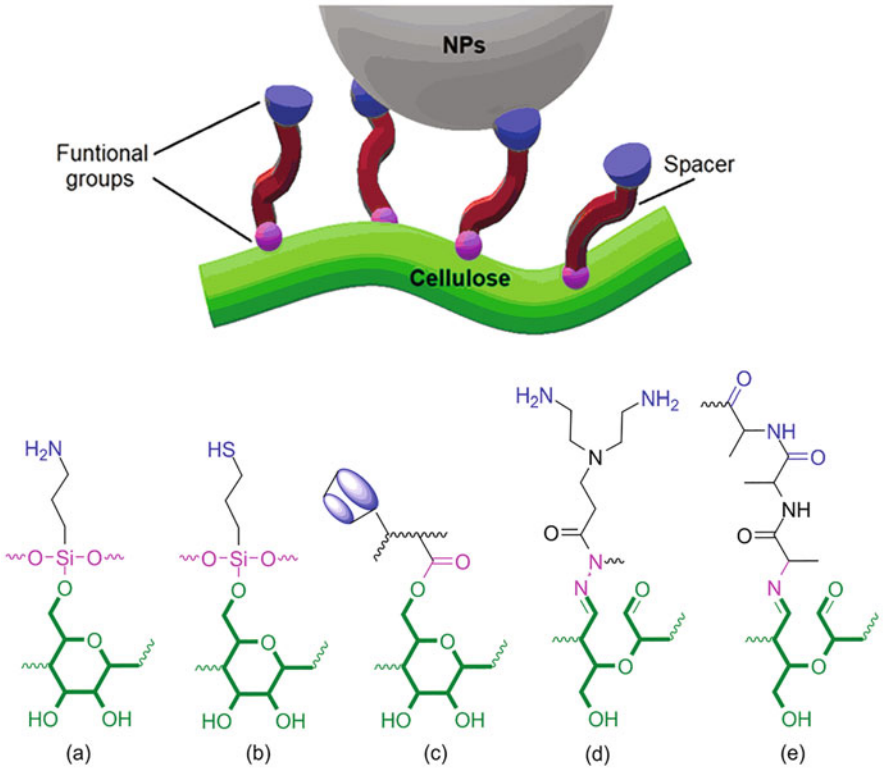

Fig. 7 Binding agents used to improve the load of NPs on cellulose

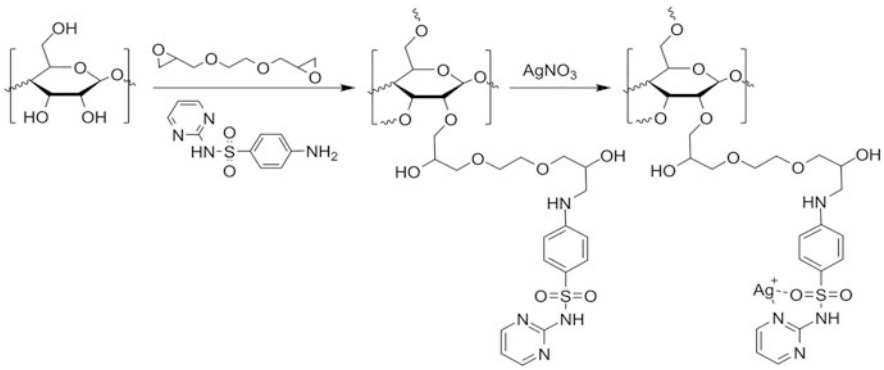

Fig. 8 Scheme synthesis of Ag-sulfadiazine coordination complex on cellulose

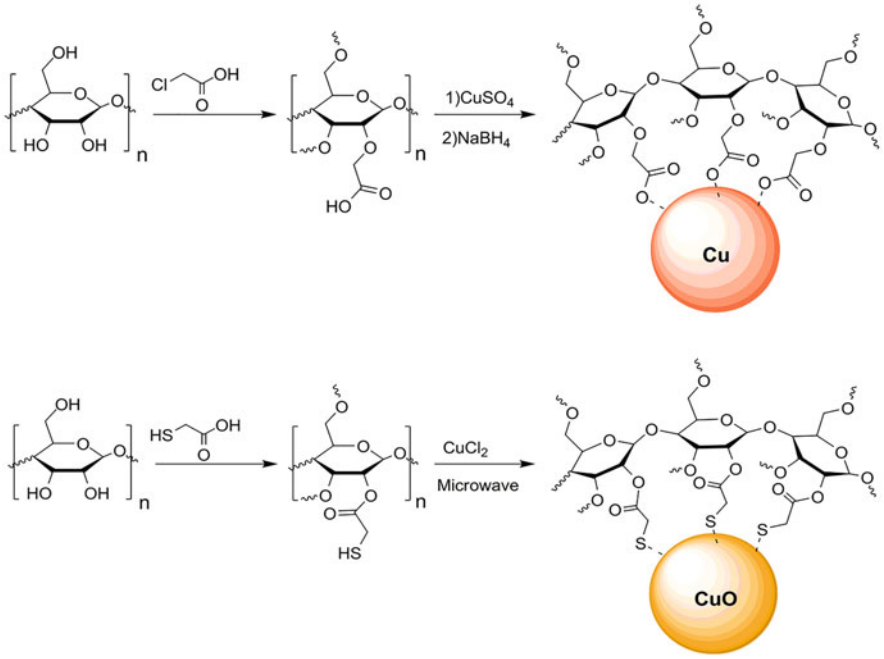

Fig. 9 Cu and CuO NPs complexed with carboxylate- and thiol-fragments on modified cotton via microwave irradiation (Gouda et al. 2015)

fabrics. The methodology is described in Fig. 8, ethylene glycol ether was used as a linking agent to bond the sulfadiazine moiety to the cellulose chain. After forming the Ag-sulfadiazine complex, the modified cotton fabrics showed a lasting antimicrobial activity after 50 wash cycles. Bioassays demonstrated that the modified cotton fabrics were biocompatible with mammalian cell lines. Also, this material may be easily reactivated with a $AgNO_3$ solution (Cao et al. 2013).

The binder not only improves the incorporation of NPs but also can stabilize them, as in the case of Cu NPs, which are loaded and stabilized by carboxylate groups to avoid metal oxidation. Also, the chemical groups integrated into cellulose allow the application of NPs nucleation methods such as microwaves irradiation as in the case of the incorporated thiol groups (Fig. 9).

ZnO is possibly the most studied inorganic compound and in the last years, ZnO NPs have got a resurgence because of its excellent antimicrobial properties and low toxicity to human cells (Shateri-Khalilabad and Yazdanshenas 2013; Bhuyan et al. 2015). ZnO NPs have additional advantages over other metal and metal oxide NPs, for example, comparing the properties of ZnO NPs with Ag NPs (i.e., UV protection, lack of staining, and costs) Zn is just standing out. However, the problems in the production of ZnO/cellulosic NPs are related to stability and antimicrobial performance. Therefore, to enhance the material stability and antimicrobial activity, cellulose must be pretreated or modified with binders.

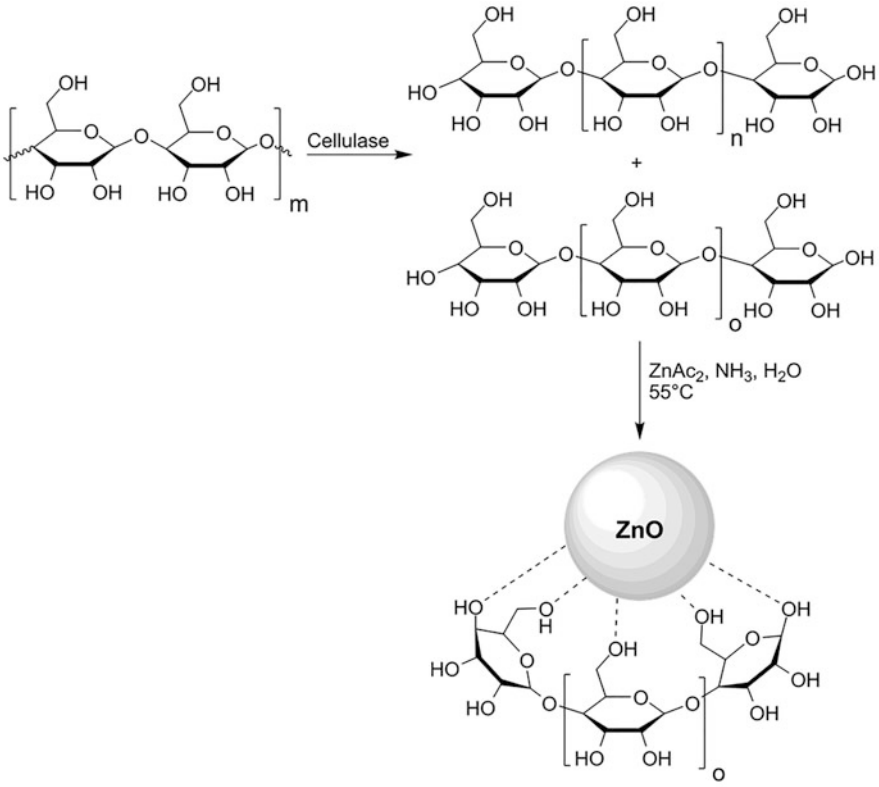

Fig. 10 ZnO NPs loading onto pretreated cellulose with cellulase enzyme (Perelshtein et al. 2012)

Polyvinyls are a type of ligands widely reported to stabilize ZnO NPs, some examples are poly-*N*-vinyl-2-pyrrolidone (PVP) (Selvam and Sundrarajan 2012), poly(allylamine hydrochloride) (Manna et al. 2013), polystyrene-block-poly(acrylic acid) copolymer (PS-b-PAA) (Çakir et al. 2012). On the other hand, natural polymers as chitosan (Perelshtein et al. 2013) and derivatives as carboxymethyl chitosan (El.shafei and Abou-Okeil 2011) are also common options in the stabilization of ZnO NPs, even natural plant extracts have been tried (Yuvakkumar et al. 2014). However, only some matrices improve antimicrobial durability (Manna et al. 2013).

The so-called cellulose pretreatment is an alternative way to improve the attachment of ZnO NPs in cellulose. When cellulose fibers are pretreated with ultrasonic irradiation and enzymes, hydroxyl groups are generated, these groups are involved during the nucleation process to yield ZnO NPs (Fig. 10). An increase in hydroxyl groups not only generates ultra-small ZnO NPs, but also promotes a uniform distribution along the cellulose fibers and an enhancement in the anchoring of the ZnO NPs. In this context, a study reported the obtention of cotton fibers loaded with ZnO NPs, which exhibited antimicrobial features (Petkova et al. 2014). In another work, a cellulosic/ZnO NPs based material was prepared by the solvent evaporation

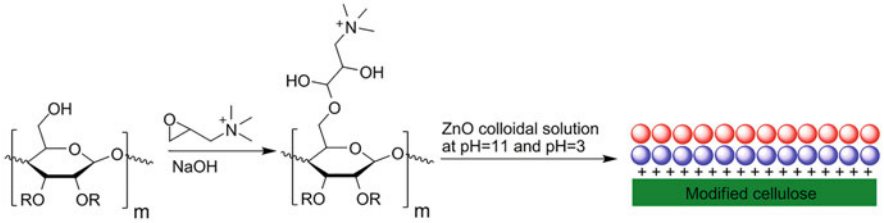

Fig. 11 ZnO loading via layer-by-layer deposition method onto cellulose functionalized with a quaternary ammonium salt

method. The obtained nanocomposites showed adequate properties as thermal stability and antimicrobial performance, regarding bacterial exposure, the maximum inhibition was achieved from the first 3 to 6 h after exposure. In general, cellulosic/ZnO NPs systems show well stability under aqueous environments, besides these materials may be designed with different shapes and sizes (Fu et al. 2015).

The layer-by-layer deposition is an option to modify cotton fabrics, for example, the endowing of cotton surface with an antimicrobial surface may be achieved by alternating layers of 2,3-epoxypropyl trimethylammonium chloride with layers of ZnO colloidal solutions, thus forming anionic/cationic ZnO NPs that after thermal treatment at 130 °C, the material showed antibacterial activity and reusability (Fig. 11) (Uğur et al. 2010).

Similarly, TiO_2 NPs are also widely used for manufacturing broad-spectrum antimicrobial cellulosic materials (Sato and Taya 2006). Also, TiO_2 NPs have photochemical properties under UV irradiation due to the formation of electron-hole pairs (Rincón and Pulgarin 2003). Also, TiO_2 NPs are reactive species that exhibit photochemical activity against microorganisms, viruses, and even cancer cells (Sunada et al. 1998; Nonami et al. 2004; Maneerat and Hayata 2006). In a study, TiO_2-coated antibacterial cotton fabrics, prepared by a sol–gel process in water, presented self-cleaning properties and were able to photocatalytic decomposition of dyes via a photodegradation mechanism (Wu et al. 2009). In this context of photoactivity, TiO_2 semi-spherical NPs (10 nm) were incorporated onto cotton to evaluate their antibacterial activity against different microorganisms under visible and black light as well as darkness to study the effect of light in the bacterial inhibition (Kangwansupamonkon et al. 2009).

3.4 Composites

Enhancing wound dressing of cellulose materials is also possible by incorporating macromolecules as collagen type I (Phisalaphong et al. 2008), alginate (Chiaoprakobkij et al. 2011), polyethylene glycol (PEG) (Cai and Kim 2010), or chitosan/lignosulfonate (Fig. 12) (Li and Peng 2015). The combination of cellulose with organic precursors preserves dermic compatibility, wettability, mechanical

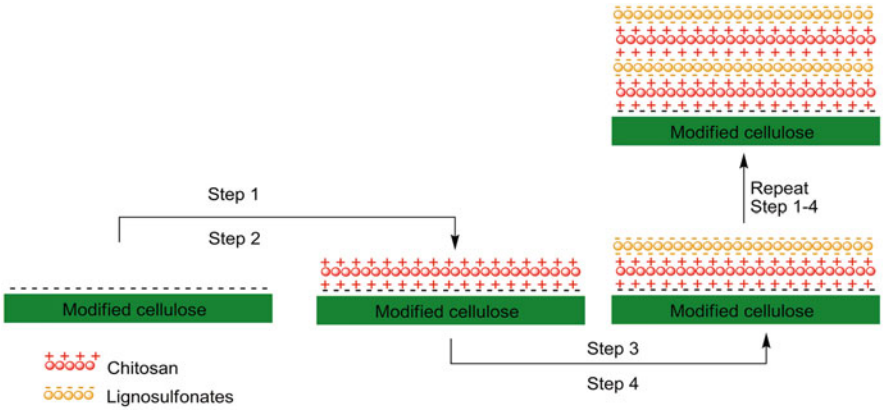

Fig. 12 Schematic representation of cellulose/lignosulfonates multilayer process on fiber surfaces (Li and Peng 2015)

strength, antifouling, and thermal stability (Chiaoprakobkij et al. 2011). In a study focused on skin tissue regeneration, cellulose–gelatin membranes were used as regeneration template (Chiaoprakobkij et al. 2011). The obtained material was combined with biocides such as benzalkonium chloride and vancomycin to develop functional antimicrobial properties. The addition of biocides was achieved by immersion of the composite in the drug solution followed by freeze-drying cycles (Wei et al. 2011).

Likewise, a composite of cellulose-chitosan-lignosulfonate was synthesized by layer-by-layer deposition via electrostatic interactions. Cellulose was oxidated by free radicals to form carboxylic groups then a layer of positively charged chitosan and negatively charged lignosulfonate was deposited as shown in Fig. 12. The result indicated an improvement in its antimicrobial activity against *Escherichia coli*, exhibiting the maximum activity when the chitosan was on the outer layer (Li and Peng 2015). In another example, a thermoresponsive microfilms composite of cellulose@nylon-6 was grafted with *N*-vinyl caprolactam by gamma-rays. The antimicrobial activity of this composite was provided by benzalkonium chloride and vancomycin loading. The biocide activity was assessed against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, exhibiting an excellent antimicrobial activity (Fig. 13). Further studies indicated that the loading of biocidal agents improved when the grafting degree increased, thus increasing the antimicrobial activity of the composite (Flores-Rojas et al. 2020).

3.5 Antimicrobial Enzymes and Peptides

Covalent immobilization of enzymes or peptides such as lysostaphin onto cellulose (Llorens et al. 2012) endows bioactivity against pathogenic bacteria like *Staphylococcus aureus* (Miao et al. 2011) or *Listeria monocytogenes* (Nguyen et al.

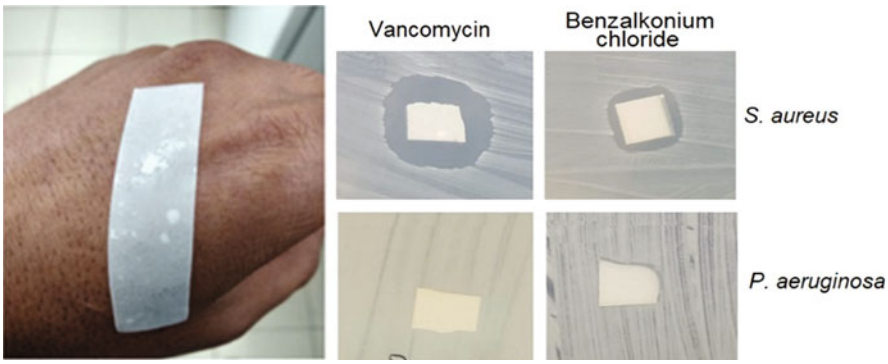

Fig. 13 Antimicrobial activity of cellulose@nylon-6 modified with *N*-vinyl caprolactam loaded with vancomycin and benzalkonium chloride

2008), the addition of natural molecules with bactericidal features allows the use of cellulose-based materials as potential candidates in the food industry as packing materials. Also, natural aminoglycoside antibiotics as gentamicin and RGDC peptides can be integrated into cellulosic materials for biomedical devices (Rouabhia et al. 2014).

Antimicrobial peptides are proteins isolated from natural sources, which despite their structure, show a cationic and amphiphilic behavior due to the hydroxyl, amine, and hydrophobic alkyl chains attached. Up to date, various models have been explored to describe the mechanism of action of peptides against bacteria (Matsuzaki 1999; Zasloff 2019). Cationic peptides are first attracted through electrostatic interactions to the bacterial surface, in a second step there is a lipid displacement that causes a disturbance in the membrane structure, and in some cases, the peptide enters into the target cell. In other cases, once the peptides reach the cytoplasmic membrane, they get attached to the cell, to finally form transmembrane pores. For instance, in a study, BC membranes functionalized with bacteriocin peptides by physical entrapment exhibited good antimicrobial activity against *Listeria monocytogenes*, a foodborne pathogen that causes more casualties than any other food pathogen (Malheiros et al. 2018).

4 Applications

4.1 Applications for Skin Tissue Repair

Cellulose outstanding biocompatibility and high water retention ability make it an excellent raw material for the manufacture of novel wound dressing materials for skin burns and chronic wounds. Moreover, cellulose works as a scaffold in the regeneration of tissues (Czaja et al. 2006; Siró and Plackett 2010). Traditionally,

most repairing materials have important characteristics such as the ability to absorb and retain exudate while in use, and non-adherence to wound due to exudate absorption followed by trauma when it is removed. A new generation of skin tissue repair materials exhibit good permeability and absorbance, also they can keep a humidity level that guarantees easy removal from the wound. However, they absorb exudate and high humidity around the wound and might contribute to the proliferation of pathogen microorganisms. In this context, cellulose-based antimicrobial materials have been endowed with antimicrobial properties, making them very promising materials in clinical applications, such as contact lenses, artificial vessels, wound dressing, cartilages, heart valves, artificial bones, among others.

Cellulose-based contact lenses have excellent oxygen permeability thus preventing hypoxia, where the most common complication is keratitis, a bacterium associated with ocular illness (Dart et al. 1991; Bourcier et al. 2003). Microorganisms involved in keratitis are *Staphylococcus aureus*, *Fusarium solani*, *Pseudomonas aeruginosa*, *coagulase-negative Staphylococci*, *Escherichia coli*, *Serratia marcescens*, *Candida albicans*, and *Acanthamoeba castellanii* (Green et al. 2008; Tu and Joslin 2010; Cerkez et al. 2011).

The load of drug in lens can provide both an eye bacterial infection and allergies treatment when drugs are maintained in an adequate concentration. For example, the loading of ciprofloxacin/γ-cyclodextrin into cellulose spawned a great prospect material for wound dressing in eye surgery, with non-adhesion properties, and antibacterial activity which inhibited growth or proliferation of bacteria on the lens surface and surrounding area, hence limiting the use of antibiotics eye drops or ameliorating in the case of eye burns symptoms (Cavicchioli et al. 2015).

4.2 Artificial Blood Vessels

Cellulose may help in reconstructive procedures associated with injuries, degenerative processes, or vascular diseases. Cellulose may be attached in the affected zone to stimulate cell growth. In this context, cellulosic composites obtained by grafting PEG onto cellulose exhibited an improved cellular adhesion. Additionally, these materials showed improved hydrophilicity since the water contact angle was reduced by PEG coat (da Silva et al. 2016). In another work, PEG-modified material was used in the adhesion of 3T3 fibroblast cells (Cai and Kim 2010). Overall, antibacterial cellulosic based biomaterials are plausible to be integrated into artificial blood vessels or heart valves.

4.3 Wound Dressing

As previously described, cellulose-based materials are excellent for wound dressing in preventing infections and helping to reduce local pain (Czaja et al. 2006). In this

context, silver/cellulose composites have been used for wound dressings due to the bactericide features of nano-Ag, likewise the use of materials containing Ag NPs has been widely reported in the inhibition of both Gram-positive and Gram-negative bacteria (Schluesener and Schluesener 2013; Li et al. 2019; Prasad 2014; Aziz et al. 2016, 2019). In this type of material, the cellulose acts as a stabilizer able to control the Ag nucleation process (Maneerung et al. 2008). Cellulose fabrics work as stabilizing agents because their porosity and hydrophilicity facilitate the growth of metal NPs (Eardley et al. 2012), these properties turn cellulose/Ag composites as prominent candidates for wound dressing and burn treatments.

5 Conclusion

In summary, cellulose is a natural polymer with the potential for the development of antimicrobial devices as well as wound healing systems. Engineering of pristine and modified cellulose structures have been extensively evaluated, the high biocompatibility and mechanical properties of derivative materials allow an easy adaptation and suggest its implementation in tissue repair and regeneration. The literature has backed cellulose as a highly versatile material, highlighting its potential for biomedical applications. Therefore, it can be assumed that cellulose will be a primordial biomaterial in the near future.

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