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Modifications of microcrystalline cellulose (MCC), nanofibrillated cellulose (NFC), and nanocrystalline cellulose (NCC) for antimicrobial and wound healing applications

https://doi.org/10.1515/epoly-2019-0013
Received August 16, 2018; accepted September 10, 2018.

Abstract: Recently, great attention has been paid to nanocomposites of cellulose, due to their unique structure as a most abundant natural polymer with having exceptional properties such as renewable, biodegradable and high specific tensile strength, aspect ratio, and Young's modulus. Prominent cellulose is naturally present in plant lignocellulosic biomass as a biocomposite made of cellulose, hemicelluloses, lignin, etc. In addition, it can be extracted from other natural sources including bacteria, algae, and sea animals. Microcrystalline cellulose (MCC), nanocrystalline cellulose (NCC), and nanofibrillated cellulose (NFC) is an emerging renewable nanomaterial that has various applications, such as food, paper production, industrial and pharmaceutical biomaterials. The surface modification on NCC can improves its disperse ability in different solvents and its utilization in protein immobilization, tissue engineering, drug delivery, and inorganic reaction template. Therefore, based on recent studies, this review illustrated considerable progresses with addressing medicinal properties involving antimicrobial and biocompatibility of nanocellulose (NC) in the case of wound healing.

Keywords: nanocrystalline cellulose; nanofibrillated cellulose**;** microcrystalline cellulose; antimicrobial activities; wound healing

1 Introduction

The most abundant biopolymer in nature, which is biodegradable, biocompatible, as well as renewable, is cellulose (1). Cellulose with a formula of $(C_6H_{10}O_5)_n$ is a carbohydrate linear polymer including repeated β-D-glucopyranose units by linkage of β(1→4) and with three hydroxyl groups per anhydroglucan unit providing high capacity of its surface modification (2). The molecular structure of this biopolymer is important as it gives the specific properties to cellulose, such as biodegradability, hydrophilicity, chirality, and high functionality (3,4). Cellulose and its derivatives, as renewable biomaterial have been more studied, focusing on their chemical, biological, as well as mechanical properties (5,6). More than 150 years, materials composed of cellulose and derived cellulose have been utilized in a wide variety of applications, such as food packaging, paper production, biomaterials, and pharmacy industry (2,7).

Introducing of nanotechnology by famous physicist Richard Feynman in 1959 has had substantial impact on other sciences and technology directly and indirectly. In this way, nanomaterials at nano (10^{-9} m) scale with unique properties such as large surface area to volume ratio have been applied in energy production, electronic, optic, catalyst, and medicine fields. Based on source of nanomaterials synthesis, there are organic, semi-organic, and synthetic nanomaterials. Moreover, nanomaterials can be in various forms such as fullerene, liposomes, dendrimer, carbon nanotube, graphene, and metal nanoparticles (MNPs) (8-12). Among these nanomaterials, NCC is a new class of nanomaterials which is obtained by acid hydrolysis, mechanical, oxidative and enzymatic treatments of cellulose fibers (13-16). NCCs compared to cellulose fibers, have more advantages, such as nanoscale dimension, high surface area, high specific strength and modulus, unique optical characteristics, etc. (1,5,17). These prominent physicochemical properties and wide prospective of application have made significant interest from both scientific researches and industry applications (18,19). In this way, usefulness of NCs applications as NFC, NCC, and also nanocomposites with other polymers was considered by food and drug association (FDA) and

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American forest and paper association (AF&PA) (20). Optical and mechanical properties of NC are unique and therefore this polymer is efficient as a building block for a various cellulosic products through self-assembly or others ways (21). Biofuels production from cellulosic materials can reduce air pollutants by reduction of greenhouse gas emissions (22,23). It can be applied mechanical or chemical methods to prepare NCs based on the crystalline nature of cellulosic materials (24). For instance, ethanol biofuel is resulted from further hydrolysis of dissolved cellulose by fermentation or catalysis. Also, Zhu and coworkers investigated on production of NFC and cellulosic biofuel by enzymatic hydrolysis of wood fibers (25).

Although, cellulose polymer has not antimicrobial activities by itself, high biocompatibility, aspect ratio (length to width ratio), and functionality degree of this biopolymer are leaded to antimicrobial application of cellulose nanocomposites with various antimicrobial agents (26). In this way, using of MNPs such as silver, copper, zinc oxide, and titania can be useful. This type of NPs has efficient antimicrobial effects on bacteria (gram positive and gam negative), fungi, and viruses (9,27,28). It is worth to noting that antimicrobial properties of the cellulose/MNPs nanocomposites in wound healing of severe burns and ulcers is important issue specifically in prevention of bacterial infections (29). Therefore, in the final section of this review, based on recent investigations, antimicrobial activities and wound healing of cellulose/MNPs with some of antimicrobial agents were presented.

2 Nanocomposite nature of cellulose

Nanocomposite of cellulose is defined as mixture of hemicellulose, cellulose, and lignin by having one or more dimensions in 1 to 100 nm (30). Integrating of these macromolecules for synthesis of larger structures is key manner for the plants survival and morphology. However, some living organisms such as sea squirts related to tunicate family, apply natural cellulosic nanostructures (20). In this case, self-assembly is a key principle of liquid crystals with establishing ability of cellulose development. Liquid crystals can be participated in the organization of another natural material such as cholesterol and biomedical diagnostics (31).

Porosity indications of the fibrillar nanostructures in natural cellulose such as hemp and cotton are one of the important aspects of these structures. In this way, pores sizes with 1 to 80 nm were determined for water swollen cellulosic fibers which prepared by sulfite pulping or kraft paper treatment (32). Firstly, bleaching and pulping increased the pores in cell walls of wood-derived fibers, but eventually high levels of lignin removal can result in overall shrinking of the material, by a reduction in average pore size (33). Refining based on mechanical processes results in augmentation of the sizes of nanopores within cellulose fibers (34), whereas pressing and drying treatments lead to close some of the nanopores (35).

3 Shapes and sizes of cellulosic structures

In the case of cellulose, the word “fibril” is common word among investigators to explain long and very thin segments of cellulosic materials (36,37). Also, the word nanofiber explains materials with very small cellulosic fibrous and functionality that differs from what has been in bulky cellulosic fibers (38). In the other words, nanofibers are commonly self-assemblies of discrete polymeric units which can have diameter of ≤ 100 nm and constitute a fiber/strand network with aspect ratio of > 1 nm (39).

As a structural material, cellulose is extremely strong, with Young’s modulus of about 250 GPa and a tensile strength of around 5200 kN-m/Kg, eighteen times more than titanium (40,41). Naturally, most cellulose is existing in plant lignocelluloses biomass as biocomposite of cellulose, hemicelluloses, and lignin (1). In order to effectively liberate cellulose from lignocellulosic biomass of elementary fibrils and nano-fibrils, advanced separation techniques are required. Also, due to production of NC from plant biomass, there are several techniques. The main process is acid treatment (acid hydrolysis), which produce the stable colloid suspensions of NCC with negative charges (42). This process has a very low efficiency around 40% and depends on various factors, such as cellulose sources, type of acid that is used for hydrolysis, reaction time, and temperature (43).

The term “microcrystalline cellulose” (MCC) is used in the case of products that have been applied for many years for pharmaceutical materials. These products can be extracted via sulfuric treatment of bleached wood fibers such as kraft paper, and then washing and drying stages (44). In this case, it has been reported that application of the spray-drying process for production of MCC generally resulted in crystals agglomeration of cellulosic elements with range shape of “stubby” to “fibrillar and small size by excess of 1 μm (45).

4 Chemical characteristics of cellulose

Structure of cellulose is based on an 180° turn-screw β-1, 4-glucopyranoside cellulose polymeric chain which rise to abundant crystalline domain formations that are considered allomorph (46). These structures have high strength more than a comparable structural of steel sample (Figure 1). Nanocrystals of these domains that are obtained by acid hydrolysis, result in intrinsic strength (47). These structures can provide reinforcement in a various composites; but, the major problem is weak interactions between polar (cellulose) and non-polar components in composites. Therefore, surface modification is highly required, which can generally be done to the cellulosic part followed by cross linking (48).

5 Sources of NC structures

5.1 Herbal materials

5.1.1 Wood

There are four major sources for obtaining of NC in nature (Figure 2). Due to its great frequency, wood can be used as precursor material for cellulose and NC extraction. Although, this process needs several stages for extraction and purification of cellulosic structures with size range within 1-100 nm (49). For instance, a method has been reported in which crushing of the water-soaked wood materials is followed by chemical treatment, mechanical refining, and homogenization in medium of liquid nitrogen temperature. Most researchers have applied slightly or almost completely purified concentration of cellulose such as MCC. In addition, other researchers have utilized bleached kraft pulp. Usually, in order to production of MCC and cellulosic nanofibers, sulfuric acid is used for hydrolyzing bleached kraft pulp. It was applied enzymatic fractionation of wood fibers for generation of nano-fibrillated cellulose and cellulose biofuel (50). NFCs with diameter size in the range 3.5-9.5 nm were extracted from fibers of *Pinus radiata* pulp by TEMPO-mediated oxidation method (51). In another approach, grinding at a high shear and pressure was applied to produce NFCs from softwood pulp fibers with porosity in the range of 29-99.7% (52).

5.1.2 Byproduct materials of agriculture

In a comparative approach, the degree of cellulose crystallinity is changed from one organism to another. For example, longer nanocrystals can be produced by algae and tunicates cellulose microfibrils, which have highly crystalline cellulose (53). Wheat stalks pulp, bamboo pulp, sugar beet pulp, potato tubers, hemp, banana, rutabaga, swede root, flax, and soybean stock as byproduct materials have been applied as source materials for production of nano-cellulosic structures (54-60). In this way, NC with density of 1.3 ± 0.03 g/cm^3, 42.3 ± 1.87 MPa, and 69.8% was extracted from wheat straw pulp by H_2SO_4 hydrolysis (43%) and ultra-sonication (30 min at 22 kGz) treatment (61). In addition, extracted bamboo nanofibrils by mechanical and NaOH-antraquinone stages in 170°C temperature were incorporated in polyvinyl alcohol (PVA) modified commercial cassava starch (FMM) as filler for enhancement of resulted nanocomposite (62).

5.2 Marine animal's NC

Important advantages of animal source for production cellulosic nanomaterials are the relative purity and suitable potential to generate almost pure NCC and NFC materials (63). Moreover, the applications of tunicate (sea animal)-obtained whiskers have been analyzed in a different methods (64). In comparison study, it has been

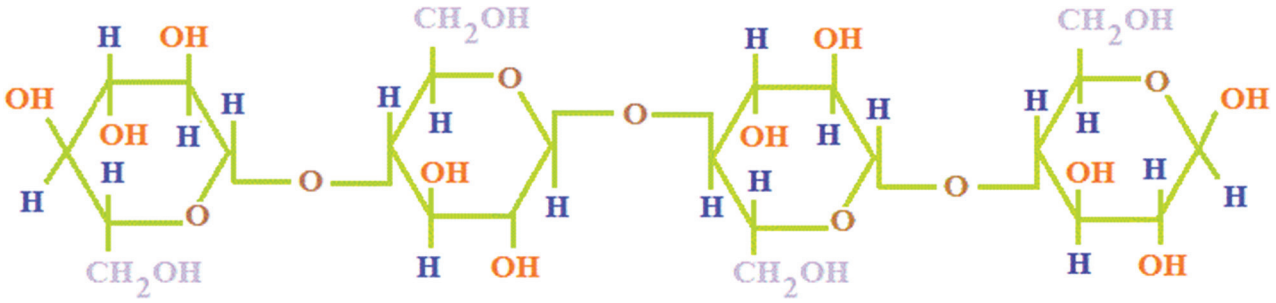

Figure 1: Structural formula of microcrystalline cellulose.

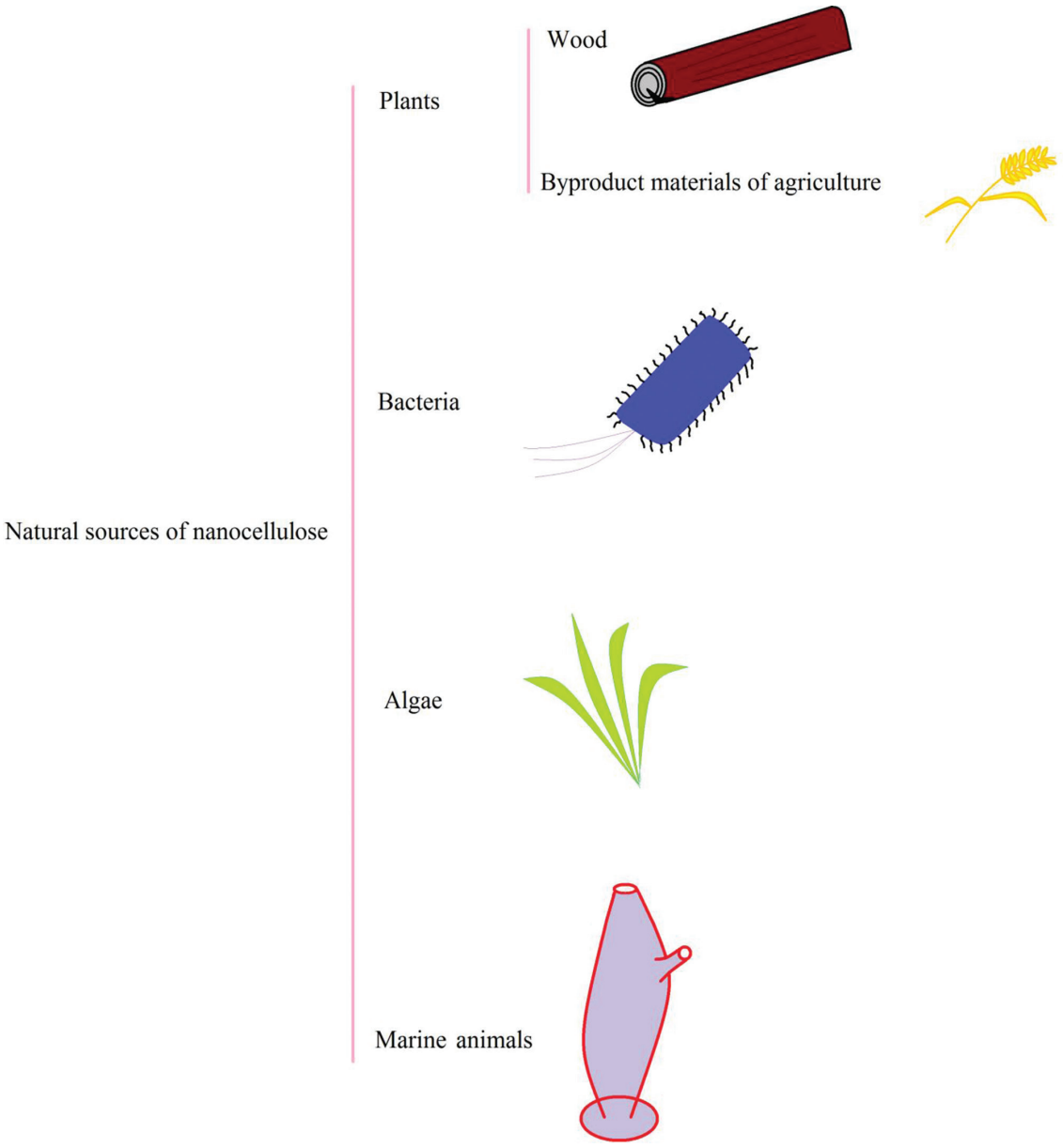

Figure 2: Natural sources for isolation of cellulose and NCs.

showed that NCC had higher quality with aspect ratio of 75 ± 60 than isolated NCC from plant (cotton pulp) and algae (seaweed) (65).

5.3 Bacterial NC

Studies on the synthesis, structure, and applications of cellulose have mainly carried out on plants, as they are the most producers of cellulose (66). Also, significant medicinal applications of cellulose structures have come from studies of bacteria (67). The bacterial-derived cellulose has several advantages such as high mechanical properties, light weight, non-toxicity, renewability, high chemical purity, and biodegradability (68). Based on a frequency of cheap carbon sources such as agro-industrial residues and wastewaters, production of bacterial cellulose (BC) represents a very interest source of cellulose nanofibers (69,70).

Synthesis of BC is an extracellular primary metabolite by bacteria of the genera *Gluconacetobacter, Agrobacterium, Acetobacter, Alcaligenes, Aerobacter, Enterobacter, Achromobacter, Pseudomonas, Rhizobium,* and *Salmonella* (Table 1). Gram negative acetic acid bacteria *Gluconacetobacter Xylinum* belonging to the genus *Gluconacetobacter* is prominent cellulose producers (71). Aerobic bacteria synthesize cellulose only in the oxygen-rich condition including on the surface of the fermentation vessel, the system becomes turbid and later a white

Table 1: Various genera of bacteria with cellulose synthesis ability.

Genus	Species	References
Gluconacetobacter	*Gluconacetobacter Xylinum*	(74)
Agrobacterium	*Agrobacterium tumefaciens*	(75)
Acetobacter	*Acetobacter xylinum(Komagataeibacter xylinus)*	(76)
	Acetobacter aceti	(77)
Alcaligenes	*Alcaligenes xylosoxydans*	(78)
Aerobacter	*Aerobacter aerogenes*	(79)
Enterobacter	*Enterobacter amnigenus*	(80)
	Enterobacter cloacae	(81)
Cronobacter	*Cronobacter sakazakii*	(82)
Achromobacter	*Achromobacter sp. CX2*	(83)
Pseudomonas	*Pseudomonas putida*	(84)
	Pseudomonas fluorescens	(85)
Rhizobium	*Rhizobium endoglucanase*	(86)
	Rhizobium leguminosarum	(87)
Salmonella	*Salmonella enteritidis*	(88)

pellicle. Optimum temperature to cellulose synthesis is around 28-30°C (72). The interior of the bacterial cell wall is region of cellulose synthesis which it spinned out from protofibrils with approximately diameter by 2-4 nm. Then, these structures are crystallized into microfibrils and bundles and later into ribbons. Microfibrils had a thickness of approximately 3-4 nm, 70-100 nm in width, and 1-9 μm in length (73). In this way, *Acetobacter xylinum* FF-88 strain was used to extract NFC with cellulose density in the range 5-1080 kg/m^3 and 28-99.7% porosity (52).

5.4 Algal NC

Algae have cellulose (cellulose Iα type) in cell wall as algic cellulose which is nearly similar to bacterial and plant cellulose and obtained after elimination of alginic acid (89). Various algae are characterized by having cellulose and NC. For example, *Cladophora glomerata* species was used as cellulose source for isolation of NFC through multi-stages process including treatment by distilled water washing, 1 wt% NaOH solution preparation, HCl hydrolysis, and filtration at 80°C. These nanomaterials had porosity range in 48-99.7% and NFC density with 5-780 kg/m^3 (52). In addition to green algae, NCC with 73% crystallinity was extracted from red algae such as *Gelidium elegans* in three stages including purification by NaOH sollution, bleaching with H_2O_2, and H_2SO_4 hydrolysis treatment (90). In similar study, it was utilized *Gelidiella aceroso* red algae species to prepare NCC by microwave pretreatment (360 W for 30 min) in alkali condition. Extracted NCC had respectively average diameter and length of 23 nm and 408 nm (91).

6 Modification of NC surface

6.1 Principles

In composites synthesis, chemical compatibility between the filler material and continuous matrix is important. The surface of cellulosic elements tends to be incompatible with many of plastic materials that are most significant in the production of composites, e.g. styrene, polyethylene, etc. Also, high ability of cellulosic fibers for absorption of water can be influenced by using various composite forms.

Surface modifications of cellulosic materials can be resulted by variety of direct reactions involving the hydroxyl groups. In this case, there are two major approaches by hydroxyl substitution and polymer grafting for covalent surface modification of cellulose (Figure 3). Esterification and silanations are two common reactions for surface modification. In addition, bifunctional reagents, polymerization, surface activation, and organometallic chemistry can be used as alternative reactions. Most of these modifications improve dispersabiliy and compatibility in different solvents or matrices. There are potential applications for modified nano cellulosic materials in variety of industrial sectors, such as nanocomposites, biomaterials, personal care, etc. (46). In this way, in below section, some of significant modifications of cellulose surface with medicinal and antimicrobial applications are presented.

6.2 Acetylation

There are several methods for acetylation and esterification of cellulose and NCC. Acetylation of cellulose may be possible via homogenous and heterogeneous conditions, which determined by solubility degree of cellulose. In according to a non-swelling reaction, the reaction only is occurring on the cellulose chains located on NCC surface. By using a simple reaction such as Fischer esterification process in single step, NCC were synthesized and functionalized at hydroxyl groups (Figure 4) (92). Susceptibility and accessibility of hydrolyzed NCC on the surface are restrictive factors on the acetylation extent. In this way, acetic anhydride ($(CH_3CO)_2O$) and acetic acid (CH_3COOH) are applied to modify the fibrous and homogenous cellulose. Both NFC and NCC were acetylated to improve physicochemical properties of NC. For example, in the case of NFC, dispersion, hydrophobicity, aspect ratio, transmittance, and thermal stability were increased for application in a flexible organic light-emitting device (FOLED) substrate (93). In this work, ratio of NFC to acetic

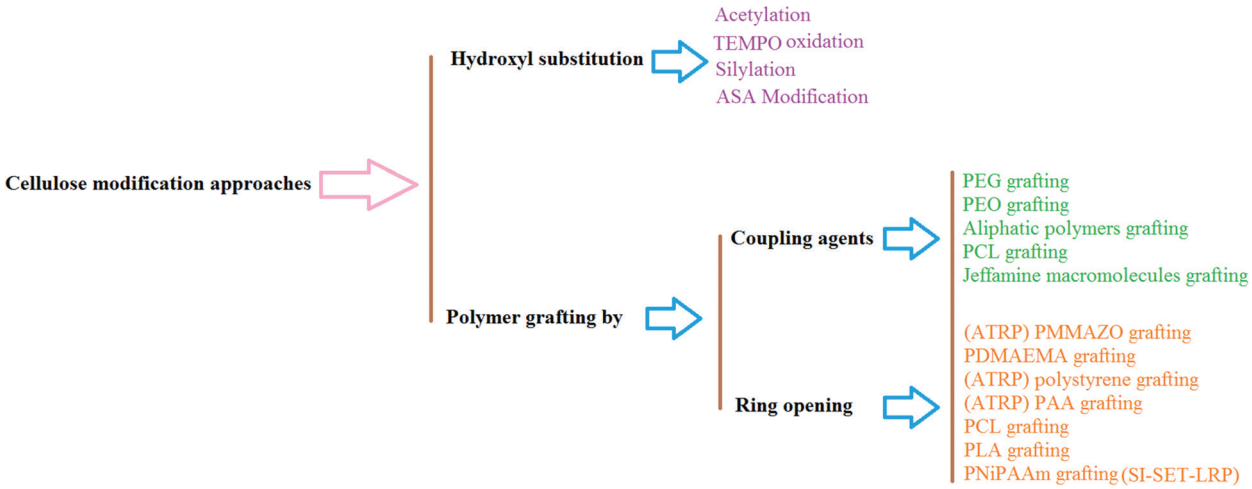

Figure 3: Modification of cellulose surface by two prominent ways. ATRP: atom transfer radical polymerization; PNiPAAm: poly(N-isopropylacrylamide); PDMAEMA: poly(N,N-dimethylaminoethyl methacrylate); SI-SET-LRP: surface-initiated single-electron transfer living radical polymerization; TEMPO: 2,2,6,6-tetramethylpiperidine-1-oxyl; PAA: poly(acrylic acid); PCL: poly(caprolactone); PEO: poly(ethylene oxide); PEG: poly(ethylene glycol); PLA: poly(lactic acid); ASA: (Alkenyl succinic anhydride).

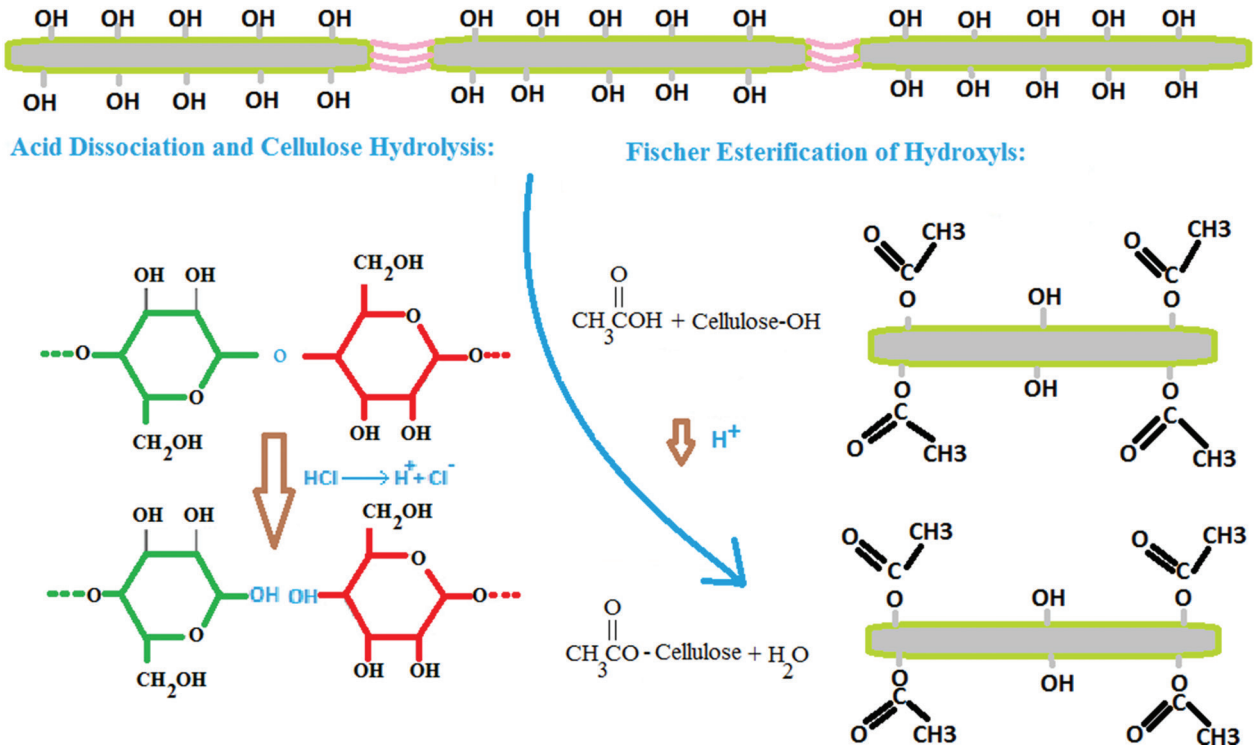

Figure 4: Scheme of cellulose hydrolysis and esterification of hydroxyl (OH-) groups via hydrochloric and acetic acids (reproduced from (92)).

anhydride was decisive factor. In another investigation, for obtaining of homogeneous acetyl CNC, acetic anhydride (AA) was added to anhydrous pyridine solution of CNC followed by heating at 80°C. Different molar ratio of AA: hydroxyl groups showed various hydrophobicity degree and mechanical values (94).

6.3 Cationization

Cellulose having hydroxyl groups on the surface has negative charge intrinsically. Therefore, cationization can be possible by addition of materials as inducer positive chargesuchasstarch,2,3-epoxypropyltrimethylammonium

chloride, and glycidyltrimethylammonium chloride. For example, cationization of eucalyptus pulps is carried out by glycidyltrimethylammonium chloride as efficient method to extract NFC. In this case, antibacterial activity of nanocomposites of cationic NFC with PVA was significant against *Staphylococcus aureus* and *Salmonella enteric* (95). In addition, hydroxyl groups of NFC were cationized via the trimethoxysilane group of (3 trimethoxysilylpropyl) phenanthridinium iodide with fluorescence properties and antibacterial effect on *E. coli*, *S. aureus*, *B. subtilis*, and *P. aeruginosa* by growth inhibition values of 17.5 ± 0.7, 15.5 ± 0.7, 12.5 ± 0.7, and 8.5 ± 0.7 mm (96).

6.4 NCC labeled by fluorescent

Fluorescence techniques were extensively used to study the cellular uptake and biodistribution of nanoparticulate delivery systems, by tracking the localization of the fluorophores. Dong and Roman described a method to label NCC with fluorescein-5-isothiocyanate (FITC) for fluorescence bioassay and bioimaging applications (97). To covalently attach FITC moieties to the surface of NCC, they developed a simple method involving three steps of reaction pathway described by the reaction route shown in Figure 5. At first, the surface of NCC was decorated with epoxy functional groups via reaction with epichlorohydrin, and then the epoxy ring was opened with ammonium hydroxide to introduce primary amino groups. Finally, the primary amino group was reacted with isothiocyanate group of FITC to form a thiourea. They compared the UV/vis absorption spectrum of unlabelled and FITC-labeled NCC in their suspensions, and found the absorption peaks of FITC in the wavelength range of 450–500 nm in the spectrum of the FITC-labeled NCC.

7 Nanocomposites of cellulose with antimicrobial agents

7.1 Antimicrobial activities

Herbal and bacterial derived NCs themselves have no antimicrobial activities. In this way, nanocomposite

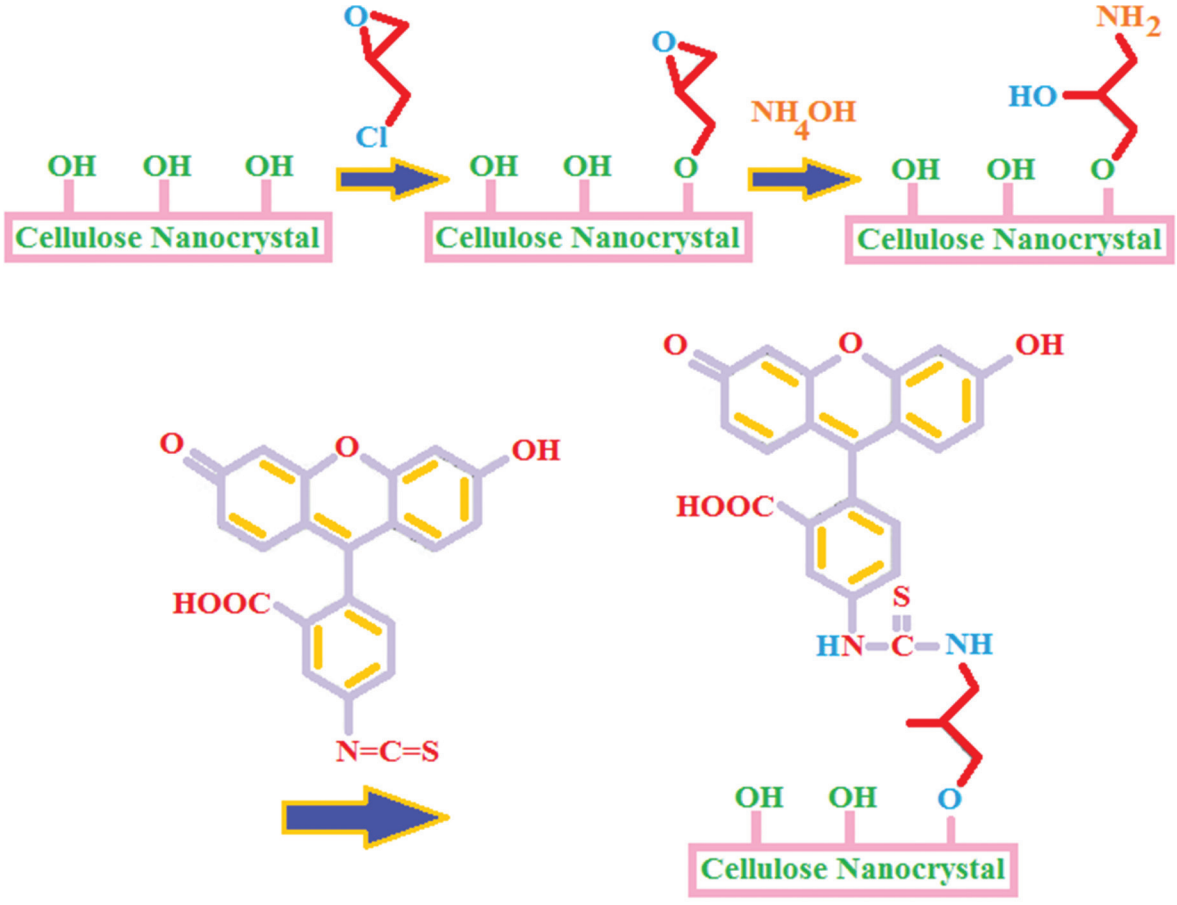

Figure 5: Reaction route for surface fluorescently labeled NCC with FITC (reproduced from (97)).

structures of NC with antimicrobial agents were applied efficiently. Higher mechanical stability and biocompatibility are two important properties which made NCs as suitable carrier for antimicrobial agents as well as scaffold in wound dressing. Based on scaffold structure of NCs, entering of pathogens is more difficult. Also, align of nanofibers in NCs structure supplies moisture condition and pores for exchange of essential gases which lead to pain reduction and increasing of wound healing (98). In the below sections, nonocomposites of NCs with antimicrobial agents were described.

7.2 Silver NPs

Biological and biomedicinal aspects of physicochemical and biogenic synthesized sliver NPs specifically their antimicrobial activities were approved by many investigations (99-103). In recent years, emerging of multi drug resistant (MDR) microorganisms with high frequency leads to offering new antimicrobial agents such as silver nanoparticles in microbial infections therapy (104). Abilities of silver NPs as antibacterial, antifungal, and antiviral are dependent on different properties of these NPs involving large surface area to volume ratio (SA:V) than their bulk material. Antimicrobial activities of silver NPs are resulted specifically from release of high reactive ions of silver (Ag^{+}) from NP surface which receive one electron from neighbor molecules to create reduced element of silver (Ag) and production of oxidized molecules or radical species in environment. As illustrated in Figure 6, this reaction in bacterial environment can influence on cell wall, cell membrane, enzymes, and genetic functions of microbes. Two factors of size and shapes of NPs are important in antimicrobial activity. As, Smaller size than larger one has higher reactivity. In addition, it was indicated that various shapes of Ag NPs involving hexagonal, spherical, and triangular showed different effects on bacterial viability (105).

Treatment of fungal infections specifically in immunocompromised patients is a heavy work because of low efficiency of antifungal drugs. In this way, presentation of novel antifungal agents by having biocompatibility and ecofriendly properties is vital. Silver NPs had antifungal activities on *Candida* spp. without cytotoxicity at 30 mg/L concentration (106). *Candida albicans* and *Aspergillus niger* demonstrated sensitivity at 25 µg/mL of minimum inhibition concentration (MIC) (107). Antiviral performance against HIV viruses at early stages of replication with functions of prevention of CD4-dependent virion binding, fusion, and infectivity was surveyed in the case of silver NPs (108).

The antibacterial activities of the Ag NPs-cellulose fibers with 0.005% to 3% w/w of silver element were significant against *E. coli* and *S. aureus* bacteria (109). Hybrid gel-membrane of bacterial CNF/silver NPs was utilized as a wound dressing nanomaterial with antibacterial effect on *Pseudomonas aeruginosa*, *E. coli*, and *S. aureus* bacteria. Antibacterial results of this study showed 1.04-2.35 mm range of inhibition zone diameters and 98.8-100% reduction in all three bacterial species (110). In another study, silver NPs are bounded on bacterial NC (BNC) synthesized from *Gluconacetobacter xylinus* strain DSM 14666. Results of this study illustrated 99% reduction in population of *E. coli* than to pure BNC (111). Antibacterial activities of the composites of silver NPs

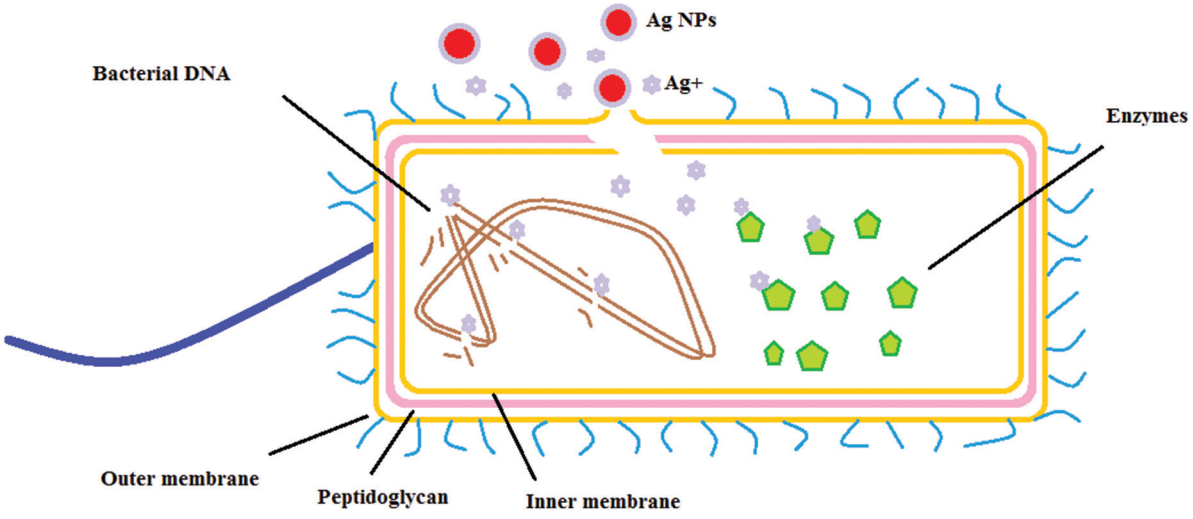

Figure 6: Basic antibacterial mechanisms of silver NPs.

and dopamine-conjugated with carboxylated cellulose nanofibers (CCNF) against gram negative (*E. coli*) and gram positive (*S. aureus*) bacterial species illustrated meaningful diameter of inhibition zones by 718.45 ± 87.17 mm^2 and 1056.57 ± 140.18 mm^2 respectively (Figure 7) (112).

7.3 Copper NPs

Antimicrobial properties of copper NPs as forms of Cu, CuO, Cu_2O, and CuS were surveyed by several investigators in vitro and in vivo (10,27,113,114). Cost effective of Cu NPs is one of their major advantages compared to Ag NPs. Lower cytotoxicity of copper than silver as an another advantage is resulted from specific function of protective mechanisms, against copper in human body (115). Copper NPs coated cellulose film showed 3-log and 4-log reduction in *E. coli* and *S. aureus* pathogens after 30 min incubation (116). Nanocomposites of Cu NPs-loaded chitosan-attached cellulose compared to cotton cellulose fibers and chitosan-attached cellulose had higher antibacterial effect on *E. coli* (117). Eight-log population reduction of *Acinetobacter baumannii* as a multidrug resistant wound pathogen was observed for Cu NPs coated cotton cellulose at concentration of 30 µg/mL with low cytotoxicity (118). Antibacterial activity of vegetable cellulose/Cu NPs and bacterial cellulose/Cu NPs composites against *S. aureus* and *Klebsiella pneumoniae* in different concentrations of Cu (% w/w) demonstrated shape, Cu content, and bacterial type dependent pattern (119). In addition, *S. aureus* ATCC 6538 showed 90% reduction of bacterial viability after 3 h incubation under treatment of Cu_2O surface modified cellulose fibers with value of 2.6 mmol Cu/kg cellulose fiber (120).

7.4 Zinc oxide NPs

Other metal NP with antimicrobial ability which was used as nanocomposites with cellulose and NC is zinc oxide NPs. As illustrated in Figure 8, preparation of ZnO NPs coated cellulose via dispersion of ZnO NPs in aqueous NH_4OH (pH=8) and remove of NH^+_4 in next step was carried out with having antibacterial activity against *E. coli* 11634 (121). Photoactivity and oxidizing antibacterial mechanisms of ZnO NPs were reported by several studies (9,122,123).

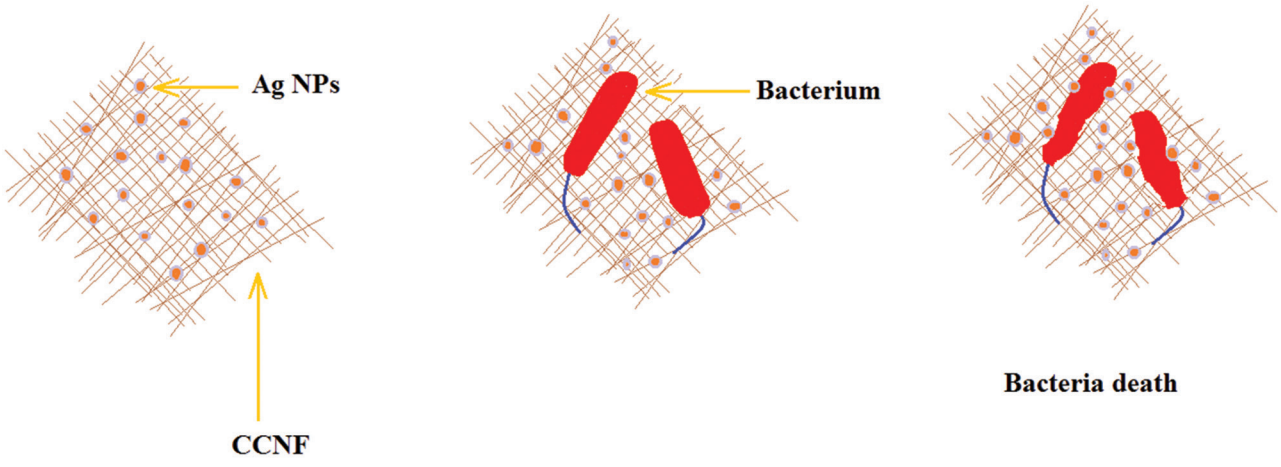

Figure 7: Antibacterial activity of the anisotropic carboxylated cellulose nanofibers (CCNF)-dopamine/Ag NPs nanocomposite (reproduced from (112)).

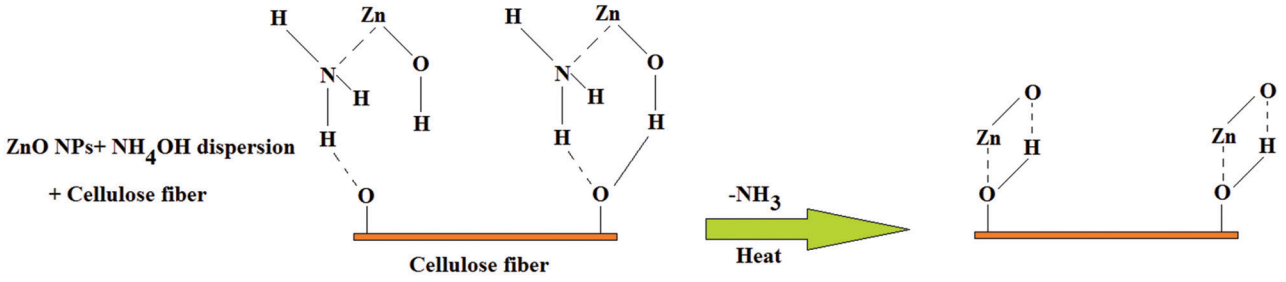

Figure 8: Schematic diagram for coating steps of ZnO nanoparticles on cellulose fibers (reproduced from (121)).

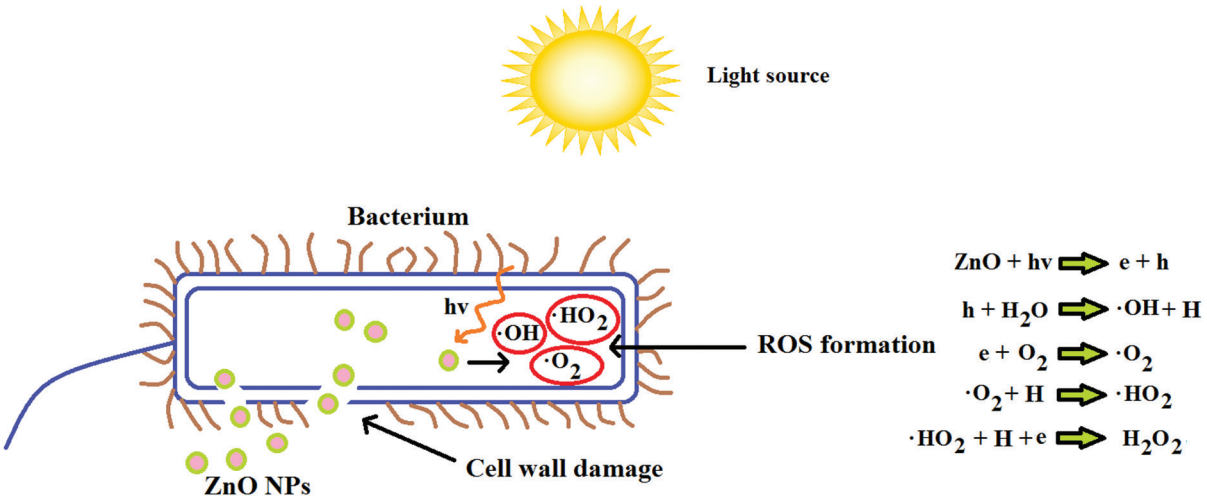

Figure 9: Antibacterial mechanisms of ZnO NPs by production of ROS (9).

Toxicity mechanisms of ZnO NPs via production of reactive oxygen species (ROS) involving hydrogen peroxide (H_2O_2), superoxide ($O_2^{\bullet}$), and hydroxide ($HO^{\bullet}$) anions are shown in Figure 9. Moreover, these mechanisms were illustrated by using electrostatic synthesized NFC/ZnO NPs/starch nanocomposites against *S. aureus*, *Bacillus cereus*, and *Klebsiella pneumoniae* pathogens (124).

In another study, NCCs were applied as a stabilizer part in nanocomposites of Zn-Ag NPs with various amounts of AgNO3 than Zn(AcO)2.2H2O as reducers. Comparatively antibacterial survey of this nanocomposite with ZnO-Ag free-cellulose showed higher inhibition zone diameter for ZnO-Ag/CNCs by higher concentration of AgNO3 (10.0 wt%, relative to Zn(AcO)2·2H2O) as values of 13.6 and 12.7 mm for respectively S. aureus and Salmonella choleraesuis bacteria (125). One-step coagulation synthesis of cellulose/ZnO NPs composites had 2-3 log, 5-7 log and complete reducing effects on E. coli after 1, 3, and 6 h incubation time (126). Ultrasound assembled ZnO NPs/bacterial cellulose films demonstrated higher antibacterial effect on E. coli and S. aureus with respectively 20.4 ± 0.00 and 7.6 ± 0.05 mm than ZnO NPs/bacterial cellulose films by 11.8 ± 0.04 and 5.6 ± 0.01 mm of inhibition zone diameter (127). Moreover, antibacterial activities of nanocomposites of ZnO NPs/bacterial cellulose against Citrobacter freundii, E. coli, S. aureus, and P. aeruginosa showed respectively 90.9%, 90%, 94.3%, and 87.4% inhibition (128).

7.5 Titanium dioxide NPs

Titanium dioxide (TiO_2) or titania is common oxide of Ti in nature with three crystal forms including rutile, anatase, and brookite (129). There are several reports related to antimicrobial abilities of TiO_2 NPs (130,131). It was illustrated cellulose/titania/chitosan/Ag NPs has higher antibacterial activities in the case of *E. coli* and *S. aureus* strains than cellulose/titania/chitosan. Antibacterial properties of titania part in these nanocomposites were resulted from bacteria adsorption onto the TiO_2 surface (132). Bacteriostatic and bactericidal effects of regenerated bacterial cellulose/TiO_2NPs on *E. coli* pathogen are caused by oxidative stress mechanism. In addition, this nanocomposite had low cytotoxicity on fibroblast cells (133). Stabilizing of TiO_2 NPs by 0.005 and 0.002 M concentration on carboxymethyl cellulose/PVA by gamma radiation illustrated respectively inhibition zone diameters as 12 and 10 mm (134).

7.6 Other antimicrobial agents

Lysozyme and allicin antimicrobial agents were conjugated with NC via cross-linker of a carbodiimide as lysozyme-conjugated NC (LCNC) and allicin-conjugated NC (ACNC). Microdilution methods of MIC_{50} and MIC_{90} illustrated LCNC and ACNC had higher antimicrobial activities than NC and lower than lysozyme and allicin antibiotics against *E. coli* ATCC 25922, *S. aureus* ATCC 25923, *Candida albican* ATCC10231, and *Aspergillus niger* ATCC 16888 strains (135). In similar study, slower release rate, antibacterial properties against *S. aureus*, and significant biocompatibility ability on human keratinocytes were observed in the case of nococomposites of octenidine-BNC (136). Food packaging with efficient antimicrobial capacity is major issue in food industry. In this way, chitosan-NC was used to package the ground meat with meaningful antibacterial effects on

E. coli, *S. enteritidis*, and *S. aureus* pathogens after 6 days of storage in 25°C temperature (137). In comparative study, loading of polihexanide and povidone-iodine antiseptic agents on bacterial NC demonstrated higher antibacterial effects of polihexanide-loaded BNC but lower biocompatibility than povidone-iodine-loaded BNC on *S. aureus* (138). Similarly, loading of laccase on BNC as nanocompsites for wound dressing application showed 92% and 26% reduction in bacterial population of *S. aureus* and *E. coli* respectively with low cytotoxicity (139).

8 Wound healing by cellulose nanocomposites

Skin organ is composed from three tissue layers of epidermis, dermis, and hypodermis (Figure 10). There are two types of wound involving chronic and acute wounds which formed resulted from thermal, physical, and chemical hurts. Wound healing or "cascade of healing" can be performed via five stages of haemostasis, inflammation, migration, proliferation, and remodeling or maturation. Healing periods for acute and chronic wounds are respectively 8-12, and more than 12 weeks (140,141). Wound healing of burns, injuries, and chronic ulcers such as diabetic ulcers is complicated issue when microbial infections are involved. Traditional, biological, and artificial dressings can be sued for wound healing. Among artificial dressing, using of natural polymers such as cellulose has major advantages of biocompatibility, biodegradability, suitable mechanical properties, and inherent permeability to water. Removal of wound dressings after healing is a hindrance in application of not degradable polymers. Biodegradability of cellulose polymer is related to function of cellulase enzyme of bacteria in nature. However, human body has not this enzyme and therefore, modified or derivatives forms of this polymer are frequently used for wound dressing. In this regard, glucose polymer of dextran was used to improve biodegradability of BC and cell proliferation in wound site (142). In another study, loading of chloramphenicol in 2,3-dialdehyde cellulose hydrogel showed higher biodegradability and drug release. Results of disc diffusion test for this study were 9, 11, and 13 mm against *E. coli*, *S. aureus*, and *Streptococcus pneumoniae* respectively (143). Bacterial infections caused by gram positive (*S. aureus* and *Enterococcus faecalis*) and gram negative bacteria (*P. aeruginosa*) are significant in single or multi-bacterial wound infections (144). In addition, sufficient moist, oxygen, temperature, growth factors, and bioactive materials are essential in fast healing of wound (145). Burn wound healing ability of bacterial cellulose/ZnO nanocomposites compared to silver sulfadiazine illustrated significant reduction in wound area as values of 66% than 77% respectively after fifteen days of treatment (128). Cellulose polymer specifically NCC and NFC with having high degree of functionality and biocompatibility are a suitable alternative for wound healing. Lu and his coworkers used sodium periodate to oxidize hudroxyl group on NFC for integration of collagen polymer. This nocomposite were prepared by cross link between amino groups of collagen with the aldehyde groups of functionalized NFC. Water absorption, porosity, and density of collagen/NFC were respectively 4000%, 95%, and 0.03 g/cm^3 (146). In another study, NC was oxidized and carboxymethylated by respectively periodate and TEMPO for using as a bioink material with growth inhibition ability in the case of *P. aeruginosa* PAO1 (147). Comparative study about mechanical and cytotoxicity of nanocomposites prepared by NCCs and chitosan polymer showed significant water absorbance with biocombatibility effect on adipose derive stem cells (ASCs) and L929 cell line after period of 7 days (148). In a different study, using hemicellulose of xyloglucan into hydrogel scaffolds of NFC resulted in meaningful reinforcement and cell growth and proliferation in 3-D matrix structure (149).

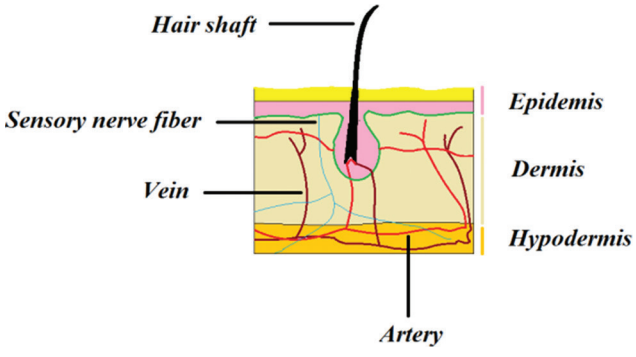

Figure 10: Schematic showing three layers with their important components of skin tissue.

9 Conclusions

In this review, natural sources and modification approaches of cellulose and NCs having antimicrobial and wound healing abilities were presented. It is worth noting that NCCs and NFCs are eco-friendly materials, which could serve as valuable reusable resources for revival forest industry specifically. New and emerging

industrial extraction processes needed to be optimized to achieve more efficient operations through active research participations from the academic and industrial sectors. The application of nanotechnology in developing NCs from the forest industry to more valuable products is required, because the availability of materials based on NCs is still limited. Increasing attention is devoted to produce NCs in larger quantities, and to explore various modification processes that enhance the properties of NCC, making it attractive for use in a wide range of nanomedicine and industrial technology fields.

Base on some of the studies which were mentioned, it is reasonable to anticipate that most successful applications of NCs, as composite form, should be formulated from water miscible matrix materials, such as PVA, latex, starch products, etc. Utilizing of cellulosic nanoelements in such applications is similar to using hydrophilic cellulose fibers for the manufacture of paper, a product that is formed in the presence of water, but which is generally in dry condition. In the case of medicinal aspects, modifications of cellulose and NCs by antimicrobial agents such as MNPs and other antibiotic substances are important processes due to improvement of wound healing property of this polymer. Although, there are many investigations in this filed, but production of defect-free materials with efficient antimicrobial, porosity, moisture absorbency in wound region is required.

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