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Exploring the Medical Applications of Nanocellulose: A Sustainable Review

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Abstract

The interesting nanomaterials that have developed quickly in the latest years and have a lot of significance in the biomedical industry are nanocelluloses (NCs). This tendency is in line with the growing need for maintainable materials that will enhance wellbeing and prolong human life, as well as the need to stay up to date with medical technological advancements. Based on the most desirable characteristics of nanocellulose, a variety of novel, useful materials with a broad scope of biomedical applications have been developed. NCs-based materials have garnered a lot of interest in medical applications due to their obtainability, biodegradability, affordability, biocompatibility, sustainability, exceptional mechanical qualities and low cytotoxicity. For the year 2022, the medical field more specifically, biosensors, drug delivery, wound dressing, tissue engineering, and medical implants, represents more than 60% of all the disciplines in which NCs are utilized. Domains, including wrapping, purification of air, ultrafiltration, elimination of pollutants, acoustics, account for around 40% of the entire number of other applications [1]. The overview of nanocellulose for medical applications is briefly reviewed in the first section of this paper. The second section explains how nanocelluloses can be modified for use in medicine. Chemically altering nanocellulose to create hydrogels, nanogels, and nanocomposites, as well as altering the surface for use in biomedicine. The review also discusses the benefits of nanocellulose over the existing technologies in the biomedical field. The final section discusses how nanocelluloses are used in the biomedical field.

Keywords

Drug Delivery, Modification, Nanocellulose, Tissue Engineering, Wound Healing

1. Introduction

The utilization of polymers, which are natural in a range of biomedicine and device materials, has remained the subject of significant research in recent years. Chitosan, alginate, gelatin, elastin, collagen, starch, also cellulose are examples of natural polymers that have drawn more attention recently for their numerous applications in pharmaceutical as well as biological fields. Cellulose in particular, has remained the focus of much research and has been employed widely in the biomedical area in recent years [2]. The most prevalent and replenishable biopolymer found in nature is cellulose. Additionally, marine organisms, including tunicates, algae, fungi, also a number of bacterial species from the families Rhizobium, Acetobacter, Sarcina and Agrobacterium, synthesize cellulose [3]. A carbohydrate homopolymer, cellulose is prepared by the units of β-D-glucopyranose which are joined by β-1,4-glycosidic bonding [4]. Since cellulose is a naturally occurring substance, scientists are also searching for its biocompatibility and biodegradability. Cellulose has been used in a variety of study domains, including those pertaining to biomedicine, energy, environment, as well as water [3]. Nano cellulose (NCs), a distinct class of engineered materials derived from cellulose, are regarded as one of the greatest auspicious green resources available nowadays [1]. NCs are appealing for a variety of uses, such as biomedical work [5], smart wrapping materials, and environmental remediation. NCs-based materials have garnered a lot of interest in medical applications due to their obtainability, biodegradability, affordability, biocompatibility, sustainability, also low cytotoxicity. Cellulose is appealing for use in filtration applications and hence can be used in filtering viruses and other bacteria [6]. An excellent option for an antibacterial substance against microorganisms is nanocellulose [7]. Nanocellulose has been shown to be one of the best materials for filtering a variety of microorganisms. Applications for the antibacterial material based on nanocellulose have grown significantly in a number of industrial sectors in recent years [8]. According to a Google Scholar study conducted applying the keywords nanocellulose as antimicrobial material, the overall numeral of articles has been trending upward over the last decade. The antibacterial substance based on nanocellulose offers a lot of promise for application as an ingredient in many different goods. For use in the medical area, researchers have been looking at the production, processing, and design of cellulose materials [9]. In keeping with the tremendous growth of nanotechnology over the past ten years, cellulose applied at the nanoscale is also being extensively investigated. Nanomaterials range in size from 1 to 100 nm, and their special properties allow for new uses [10]. Three forms of nanocellulose, including bacterial cellulose (BC), cellulose nanocrystals (CNC), also cellulose nanofibrils (CNF) may be separated from innate cellulose. The latter is a material that shows promise for utilizing in tissue engineering scaffolds also implants [9]. Plant cell walls can be used to harvest cellulose nanocrystals and cellulose nanofibrils. Fibres and fibrils are hydrolyzed with acid to create the first form of nanocellulose fibres. The amorphous areas are broken down by this process, producing extremely crystalline nanoparticles. On the other hand, high shearing homogenization at high pressure is used to mechanically induce destructuring in order to produce cellulose nanofibrils

[11]. Bacteria produce bacterial cellulose in a pure form, devoid of any contaminants. Chemical functionalization of nanocellulose surfaces with bioactive compounds is being researched to enhance interactions with the human body [9]. These days, commercially marketed nanocellulose-based wound-healing solutions include Bioprocess®, XCell®, Biofill®, and Nanoskin® [12]. Numerous nanomaterials based on cellulose have been produced for use in the field of biomedicine mostly in the past ten years, with an estimated $97 billion in influence on the medical and life sciences sector [9].

This review focuses on the utilization of nanocellulose in the biomedical field. Mostly, concentrates on the utmost current advances found with regard to nanocellulose as antibacterial material, medical implants, wound healing, drug delivery, regeneration of bone-cartilage also dental application. The explanation of cellulose potential utilization in the field of biomedicine is preceded by the presentation of cellulose structure and types/chemical reforms of cellulose applied in biomedical studies.

2. Modification of Nanocellulose for Antimicrobial Materials

Nanocellulose cannot inhibit wound infections in humans on its own because it is not an antibacterial agent [9]. **Figure 1** illustrates how surface modification with biocidal chemicals can create nanocellulose-based antimicrobial materials that are effective against wound infection [13]. The meanwhile, surface functionalization can be accomplished via a variety of techniques involving the chemistry of the hydroxyl function, such as esterification, etherification, also oxidation [14]. This will support nanocellulose to contain a variety of functional groups, including quaternary ammonium also the aldehyde group, which give them their biocompatibility and bacteriostatic qualities [7]. Other cellulose conjugation agents for antibacterial characteristics were identified by Alvarado *et al.* (2019) [13]. These agents included chitosan, silanes, chlorine, and metal/metal oxide tiny particles (e.g. gold, silver, copper, copper oxide, magnesium oxide, zinc oxide, and titanium dioxide).

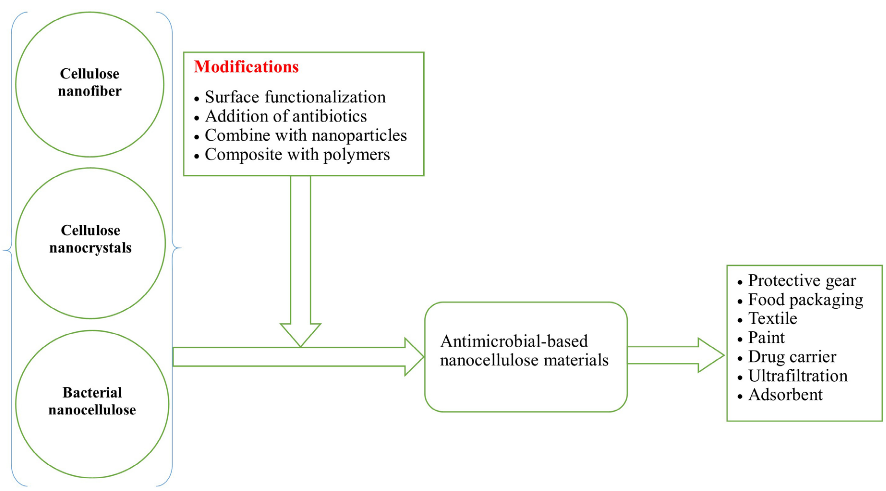

Figure 1. Synthesis and application of nanocellulose-based antimicrobial material [8].

Nanocellulose typically has a variety of substances added to it, including quaternary compounds, aldehydes, antibiotics, as well as tiny materials. Typically, oxidants like periodate sodium and 2,2,6,6-teramethylpiperidinyloxy (TEMPO) are utilized to graft the aldehyde groups on nanocellulose. In aqueous circumstances, TEMPO may attach to the nanocellulose's surface, changing the OH group at the C6 location into aldehyde also carboxyl functional groups. Numerous antibacterial applications have demonstrated the remarkable potential of aldehyde-nanocellulose. An example of functionalizing nanocellulose with numerous quaternary chemicals for antiviral utilization is shown in Figure 2. Altering the surface charge of nanocellulose will assist to increase the electrostatic interaction capabilities because the majority of viruses also certain other microorganism species typically possess a charge on their surface. This is crucial to creating a filtering material with great efficiency. Antibacterial compounds based on nanocellulose are often produced using antibiotics. Typically, this technique is used for packaging also biomedical applications. Particularly for bacteria, inorganic nanoparticles like metal and metal oxide tiny particles are frequently utilized in antimicrobial materials based on nanocellulose. They come into touch with the bacteria after being released from the composites. Inorganic nanoparticles comprising nanocellulose-based materials have a substantially lower threshold inhibitory concentration than single metal or metal oxide nanoparticles, demonstrating their significance and advantages in a variety of applications, including wound healing [8].

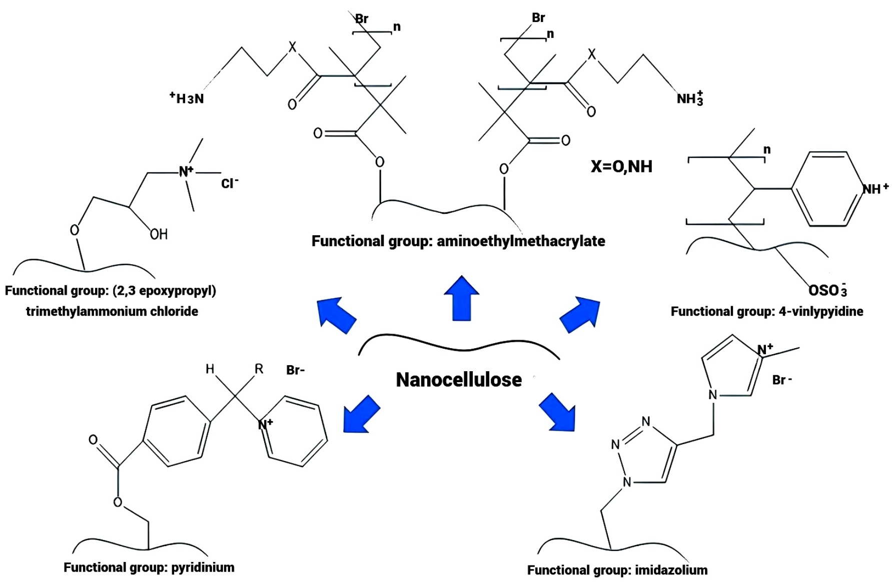

Figure 2. Graphic representation of an example functionalization of nanocellulose with quaternary compounds [8].

2.1. Chemical Modification of Nanocellulose for Biomedical Applications

Chemical changes to nanocellulose can result in by-products with broader uses. Convinced functional groups are added during modification in order to enhance compatibility, particularly when combined together with non-polar or hydrophobic media in nanocomposite materials and to rise the quantity of steady positive or negative charges for improved dispersal [15]. Acetylation and carboxy-methylation are two of the most prevalent chemical changes, as explained below. Acetic anhydride in acetic acid is used to create cellulose acetate (CA) [16]. When hydroxyl groups are swapped out for carboxymethyl ones, carboxymethyl cellulose (CMC) is created. The resulting product is used in biomedical field [3]. Nanocellulose, both using and without using chemical modification, is appealing for numerous biomedical applications due to its established biocompatibility and significant absence of significant negative effects in an animal model [17].

By applying a silver nitrate precursor to the surface of BNC and reducing it in situ, silver nanoparticles may be incorporated [18]. Silver nanoparticles may be chemically bonded as narrowly distributed particles while preserving the high crystallinity of BNC using a photochemical reduction process in the presence of UV light [19]. Additionally, in situ ultrasonic synthesis is used to insert the antibacterial ZnO nanoparticles into BNC [20], allowing for the formation of nanocrystalline nanoparticles in conjunction with BNC's high crystallinity. According to the findings, the chemically altered nanocellulose was most effective against both Gram-positive and Gram-negative pathogens. As a result, improved antibacterial qualities over time may be guaranteed [21].

2.2. Advanced Functional Materials Based on Nanocellulose

2.2.1. Nanogels

The features of gels and colloids are combined in nanogels, also called hydrogel nanoparticles [22]. They are typically spherical in form then range in size from 20 - 200 nm. Because they combine the benefits of nanoparticles with the properties of hydrogels, hydrogels at the nanoscale have enormous promise for use in biological applications, such as drug delivery systems [23]. The hydrophobic medications' solubility is improved, cytotoxic side effects are decreased, accumulation of drug in tumours is improved, and therapeutic agents are more stable against enzymatic and chemical degradation when hydrogel particle sizes are reduced to the nano range [24]. The capacities of drug-loading are high, chemical steadiness, mechanical qualities that prevent disintegration or else fracture in the course of transportation, also sensitive response behaviour that guarantees rapid drug release in response to pertinent stimuli are some of the other desirable characteristics of the nanogels [23]. Other biomedical fields, including chemotherapy [25], disease diagnosis [26], vaccine delivery [27], biocatalysis [28], also the creation of scaffolds that are bioactive in renewing medicine [24], have also found use for nanogels due to their exceptional suitability in the drug delivery field. Additionally, they have been investigated for gene and protein delivery [26] and diabetes therapy [29]. Natural nano-hydrogels have garnered lots of interest due to their numerous applications in drug delivery, medicine, tissue engineering, pharmacy, also cancer treatment [30]. A long-sought objective that has been accomplished for several hydrogel types is the utilization of tiny-cellulosic materials to create hydrogels from renewable resources [31]. There are numerous good hydrogels types based on nanocellulose that have been established with potential aimed at use in biomedical applications, including injectable hydrogels [32]. Nevertheless, nanocellulose compounds do not gel by themselves [33]. For instance, there are various methods for gelating CNC suspensions, including merely increasing the suspension's concentration by decreasing the electrostatic double-layer distance [34], altering the solvent conditions by increasing the ionic strength [35], adding polymers [33], sonicating [36], and hydrothermally treating at a high temperature [31]. High stiffness and relatively low anisotropy make nanocrystalline cellulose ideal for use as templates for aligned structures while offering flexibility and robustness. For example, collagen provided networks with good biocompatibility and mechanical characteristics akin to those of ligaments and tendons [37]. Nanofibrillated cellulose (CNFs) refers to the kind of nanocellulose that is furthermost likely to create hydrogels. Compared with gels produced by CNCs, CNFs produce gels with significantly more elasticity. At concentrations between 0.05 and 6 weight percent, CNFs will provide such structures [37]. Pure CNFs provide the most straightforward example, forming hydrogels on their own due to their length and interacting entanglements [23].

2.2.2. Hydrogels

Hydrogels are currently vital as biological active implants in the logic of "in vivo" scaffolds and have advanced to imitate fundamental physiological processes. Large amounts of water may be absorbed and retained in an aqueous environment by hydrogels, which are three-dimensional network colloidal gels made of hydrophilic polymers that have been cross-linked by swelling [22]. They have a rubbery, squishy texture when enlarged, which is similar to how extracellular matrix (ECM) behaves in real tissues [38]. Additionally, when applied on various surfaces, hydrogels may adapt to them. The favorable candidates for biomedical applications due to these qualities in addition to their muco-adhesive nature, elasticity, swelling, also de-swelling features in response to environmental stimuli are hydrogels [22]. Contact lenses [39], blood-contacting hydrogels [40], wound-healing bioadhesives [41], artificial kidney membranes [42], artificial skin [43], vocal cord replacement [44], and artificial tendons [45], are just a few of the materials that hydrogels have been used to create.

2.2.3. Nanocomposites

Research on hydrogel tiny-composite materials, comprising functionalized tiny-particles, is likewise advancing at the minute. Generally, polymeric matrices of tiny-composites are supplemented with nanoparticle materials or nanofillers to enhance or alter certain characteristics. In particular, hydrogels are coupled with nanoparticle materials that provide magnetic or antibacterial properties, or they are strengthened with tiny-scale materials to create nanocomposite materials with excellent mechanical strength features [22].

2.3. Comparative Information on the Performance of Modified Hydrogels with Traditional Hydrogels

The advantages of modified hydrogels over conventional hydrogels in wound healing depend on their ability to behave as a human skin replacement, offering both therapeutic benefits and a protective barrier which is not offered by conventional hydrogels [46]. Because of their unique qualities, which include high moisture content and suitability for wounds, high porosity and a large surface area for cell interaction and growth, high tolerance to adhere to irregular skin, and the creation of a physical barrier against external bacterial infections, modified hydrogels are mainly used as wound dressing materials [21]. Modified hydrogels' properties and interactions with the skin provide a transient epidermal replacement that enables heat injury re-epithelialization [47].

3. Surface Modification of Bacterial Nanocellulose for Biomedical Applications

To add certain qualities necessary for biomedical utilization, bacterial nanocellulose's surface must be modified. **Figure 3** provides a summary of the features needed for biological applications as well as potential functionalization techniques. It is possible to alter porosity, surface topography, and wettability concurrently using chemical surface modification. As an alternative, BNC membranes might be modified physically using techniques like gamma irradiation to adjust surface characteristics and increase pore density, which could result in slower drug delivery diffusion processes [21]. Chemical surface modification of nanocellulose is often done to provide hydrophobic qualities. Common surface modification methods, including grafting chemically to increase compatibility with an extra hydrophobic matrix, are comparable to modification pathways utilized in nanocellulose manufacturing [21]. Physical methods, surface modification with chemicals, and polymer graft co-polymerization are all part of the conventional hydrophobization of nanocellulose. BNC membranes may now be treated with plasma to increase their hydrophilicity in plasma that is cold using nitrogen or sources of amine [48], form hydrophobic characteristics with carbon fluoride pioneers, or else generate silanization with oxygen plasma [49]. However, as seen below, more surface adjustment of BNC is necessary for biomedical applications in order to better control cell contacts and regulate antibacterial characteristics. The comparatively high hydrophilicity and bio-affinity of BNC membranes promote their surface affinity for cell attachment and growth. BNC lacks the inherent ability to start cell attachment despite its minimal toxicity and biocompatibility. Specifically, the inherent biological activities of proteins are absent from the polysaccharide structure of BNC.

A second review was conducted on the function of surface adjustment in biomedical as well as medical applications [50]. By linking with growing factors and extracellular matrices, BNC's biocompatibility may be further enhanced. At the same time, the BNC's microstructure permits decent integration of steady interconnective channels [21]. Specifically, the addition of amino acids to bacterial nanocellulose enhances cell adhesion and biocompatibility as it promotes proliferation of cell, also intervenes cell interactions whereas improving tissue biocompatibility. Furthermore, the open porosity structure and strong connection amid the protein and the open cellulose membrane structure of bacterial nanocellulose/fibroin composite membranes resulted in improved chemical and mechanical steadiness. In addition to being biocompatible, BNC's elastomeric and anisotropic qualities that is, its high elasticity were improved to make it more appropriate for tissue engineering. Additionally, BNC and gelatin hybridization improved the growth and proliferation of cell, making the hydrogel which is modified a viable option for clinical diagnostics, tumour tissue engineering, and cancer research using in vitro grown tumour cells [51]. Following immunocytochemical examination, the fibronectin also collagen were immobilized as adhesion proteins onto bacterial nanocellulose, then their high compatibility was proven [52]. Cell-derived proteins, including IKAV peptide sequences, were immobilized on bacterial nanocellulose fibers to decrease wettability and improve thermal steadiness. Furthermore, BNC's antibacterial qualities must be enhanced for usage as innovative wound dressings. Natural additives like honey derived from various plants were used to improve the antibacterial qualities of BNC. Thyme had the strongest effectiveness against both Gram-positive and Gram-negative pathogenic bacteria, according to the results [21].

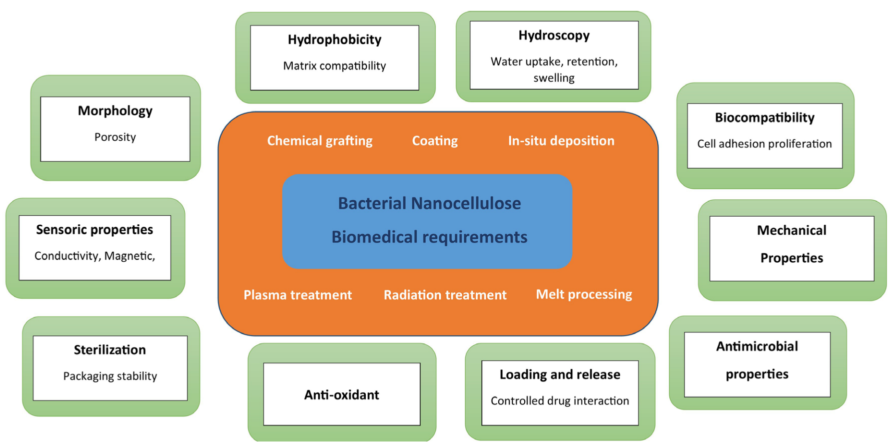

Figure 3. Unique properties and functionalities offered to bacterial nanocellulose through surface modification, as required for biomedical application [21].

3.1. Challenges in Scaling Up the Modification Techniques for Nanocellulose for Biomedical Applications

Good control of BNC's structure and characteristics is necessary for its inclusion in useful biological applications. Since dried BNC lacks functional groups in its natural state, controlling its rehydration characteristics is another issue. For the cellulose fibril chains to form carboxyl bridges and avoid condensation during drying, further surface modification is necessary [53]. The high cost and low yield of BNC manufacture are two more significant obstacles. Despite the availability of the initial commercial production grades, it is imperative that industrial production be further optimized under circumstances that are economically relevant [54]. As a result, a lot of recent research has concentrated on raising yields and enhancing production efficiency to meet the growing demand for BNC in a variety of applications [21].

3.2. Difference between the Advanced Functional Materials Based on Nanocellulose Materials and Existing Biomedical Technologies

The mechanical characteristics of nanocellulose, such stiffness and tensile strength, also differ greatly based on the kind of nanocellulose and how it is processed, enabling customized material design for particular uses [55]. Numerous sites for chemical modification are made possible by the presence of hydroxyl groups on the surface of nanocellulose, which enables the attachment of different functional groups like growth hormones, medicines, or targeting ligands. Materials based on nanocellulose may be designed with specific qualities and functions thanks to this adjustable surface chemistry. Targeting ligands, for example, can improve drug delivery systems' selectivity by guaranteeing that the therapeutic substance reaches its target without harming other organs [56]. In tissue engineering applications, growth factor incorporation can also encourage cell adhesion, proliferation, and differentiation [23]. Nanocellulose differs from many other biomaterials in that its surface chemistry may be controlled, which makes it possible to create highly targeted and efficient biomedical devices.

Conventional drug delivery methods frequently have drawbacks such unpredictable release patterns, quick clearance, and non-specific distribution, which can lead to negative side effects and decreased therapeutic effectiveness. Systems based on nanocellulose provide notable advancements in these fields. Effective drug loading is made possible by nanocellulose's large surface area, and regulated release kinetics are made possible by its adjustable surface chemistry [57]. This stands in stark contrast to many traditional approaches that depend on systemic administration, which frequently cause medication distribution to unexpected locations. Diffusion-controlled release from porous nanocellulose matrices and stimuli-responsive release, which is triggered by variations in pH, temperature, or other environmental conditions, are two examples of the several release mechanisms that may be used [58]. Additionally, tailored medication distribution to certain cells or tissues is made possible by surface modification with targeting ligands [56], reducing off-target effects and improving therapeutic effectiveness. This focused strategy lowers the chance of side effects and greatly enhances treatment results. Traditional wound coverings generally lack antimicrobial characteristics and may inhibit healing, resulting to extended recovery periods and increased risk of infection. In this regard, dressings based on nanocellulose provide notable benefits [55]. Nanocellulose's natural biocompatibility encourages tissue repair and reduces inflammation [57], and its large surface area enables the addition of antimicrobial substances like antibiotics or silver nanoparticles [59]. This lowers the chance of problems by improving wound healing and preventing infection. The development of dressings with superior moisture retention and breathability is made possible by the ability to produce hydrogels and aerogels from nanocellulose which fosters a favourable wound environment and speeds up healing. Compared to conventional gauze and bandages, these properties offer a significant improvement that promotes quicker healing and less scarring [23].

3.3. Benefits of Nanocellulose over Conventional Materials in the Biomedical Field

BNC's functionalization and alterations increase the possibility of topical or active wound healing. It has been acknowledged that the modified BNC is a highly effective polymeric carrier for therapeutic wound healing [60]. Rehabilitating large wound areas with effective healing and a minimal inflammatory response in comparison to traditional materials indicated the rapid healing process using BNC [61]. To further reduce wound healing time, a BNC/sericin membrane was impregnated with a solution that promotes fibroblast growth and extracellular matrix synthesis [62]. With the addition of polyhexamethylene to BNC/sericin membranes, collagen formation, cell migration, and irritation were all encouraged, wound size was quickly reduced, and wound infection was avoided [63]. BNC's ultrafine morphology, mechanical durability, biodegradability, non-toxicity, high water retention capacity, and reactivity for chemical modification are among of its unique advantages in biomedical sectors [64].

4. Advanced Nanocellulose Materials for Biomedical Applications

4.1. Antimicrobial Activity

The antibacterial and/or antimicrobial characteristics of cellulosic materials are obviously not inherent. The development of new functional biomaterials based on cellulose by adding antimicrobial/antibacterial activities by the functionalization and/or inclusion of antimicrobial/antibacterial means is of tremendous interest due to the vast potential of cellulose materials. For example, N-halamine also nanocurcumin have been incorporated into the network of cellulose to create antimicrobial nanocellulose-based materials, and aminoalkyl groups, L-cysteine, 2-benzyl-4-chlorophenol, and diclofenac have been chemically grafted onto the cellulose backbone's surface [2]. To improve the effectiveness of its antibacterial qualities, nanocellulose must be modified via surface functionalization [8].

A combination of poly(3-hydroxybutyrate) and nanocellulose treated with zinc oxide tiny-particles was created by Panaitescu *et al.* (2018) [65] to improve its qualities and antibacterial action against *Escherichia coli* as well as *Staphylococcus aureus*. According to **Figure 4**, treatment of nanocellulose by zinc oxide plasma completely inhibits the development of *Staphylococcus aureus*. The combination of CNC together with chitosan for coatings of tissue for antibacterial also superabsorbent tissue sheets has been shown by Tyagi *et al.* (2019) [66]. 99 percent of *Escherichia coli* growth can be inhibited by this modified nanocellulose. **Figure 5(a)** illustrates this process's mechanism. Because chitosan is included, the surface of material produced is positively charged. In contrast, the cell membrane of *E. coli* is negatively charged. This makes it possible for the created material and *Escherichia coli* to interact electrostatically. In addition, after being adsorbed on the surface of the material produced, the stiff and thin CNC particles would harm the cell membrane. Furthermore, because of the osmotic imbalance in the cell, the approachability of chitosan into the membrane of the cell would result in additional damage also denature the cell membrane [8].

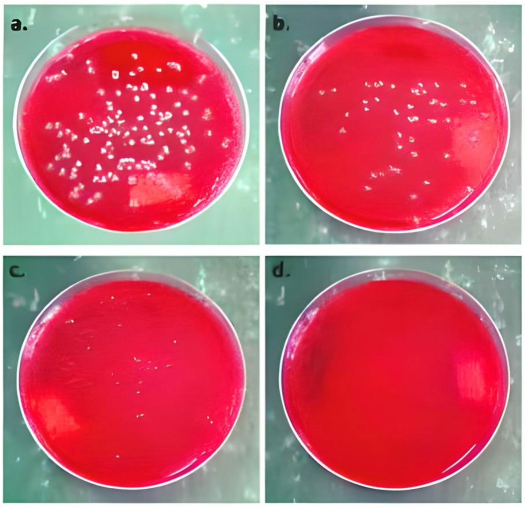

Figure 4. Antibacterial activity of nanocellulose composite films against *Escherichia coli* (a) before the plasma treatment and (b) after the plasma treatment; and against *Staphylococcus aureus* (c) before ZnO plasma coating and (d) after ZnO plasma coating [8].

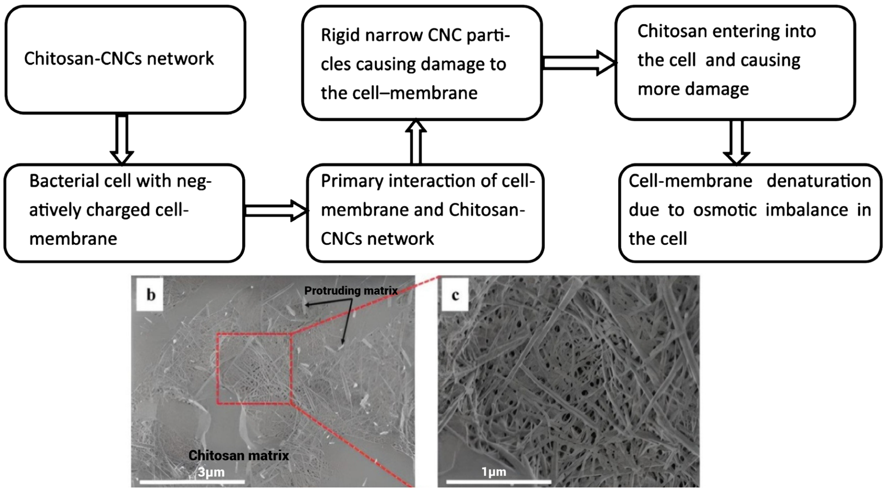

Figure 5. (a) Graphic representation of the theory of using nanocellulose and chitosan together for antimicrobial and superabsorbent tissue papers. The chitosan–CNC composite at diverse magnifications: (b) 15 000× and (c) 50 000× [8].

4.1.1. Nanocellulose as an Antimicrobial Material for Viruses

Developments in nanotechnology have sparked interest in creating virus elimination filters based on nanocellulose, with an emphasis on adsorptive filters that work through electrostatic interactions rather than size exclusion. One of the most important processes in clinical and biopharmaceutical applications is the ensnaring of viruses. The safety of plasma-derived biopharmaceutical products is really threatened by viral contamination, which emphasizes the necessity of implementing virus contamination control measures. To the best of our knowledge, filtering is often the reason behind the creation of antiviral compounds based on nanocellulose. A proven, dependable, and durable technique for physically eliminating all forms of infectious microbes, including viruses, is size-exclusion-based viral filtration [8]. Viral filtration based on size-exclusion features a sophisticated internal pore network that may quantitatively transport molecules smaller than 15 nm, according to Kosiol *et al.* (2019) [67]. As a result, mostly by size exclusion, at best 99.99 percent of the bigger microbes, comprising viruses would be kept. Numerous elements, including size of the pore, thickness, virus size, filter surface charge, number of layers, ionic strength, and surface chemistry, might influence how effective the process of filtration is [6]. According to Metreveli *et al.* (2014) [6], **Figure 6** illustrates how the Swine Influenza A Virus (SIV), with particle size between 80 - 120 nm, was successfully eliminated by a nanocellulose filter. On the porous filter paper's surface, a layered arrangement of the latex beads and Swine Influenza A Virus particles is visible. It has also been shown that altering the surface of nanocellulose increases its ability to filter out viruses. For instance, it is known that the surface of the coronavirus and a number of other viruses is negatively charged [68]. The structure of the coronavirus is seen in **Figure 7**, where proteins with lipid head groups which are negatively charged are inserted in the bilayer. The virus will be successfully trapped on the nanocellulose because of the electrostatic attraction between the positively charged nanocellulose and the negatively charged virus.

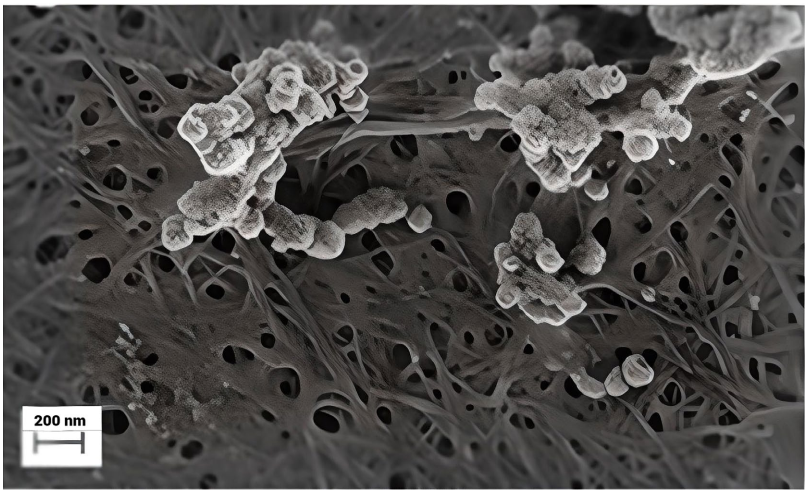

Figure 6. SEM image of SIV filtration on a nanocellulose membrane [8].

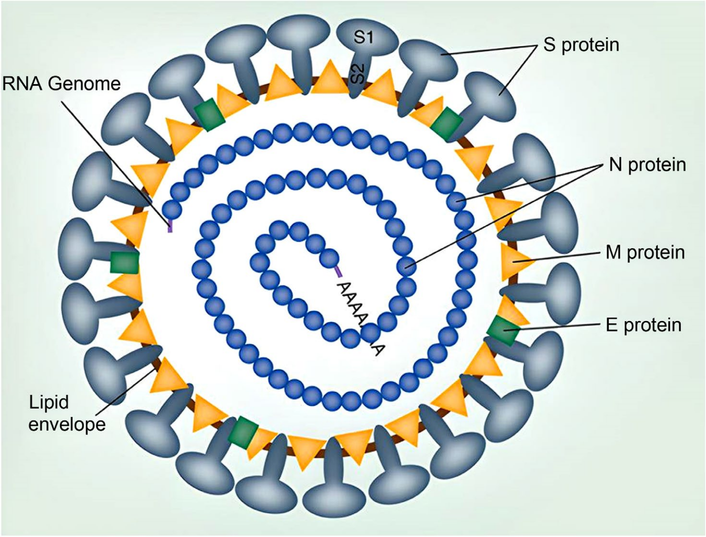

Figure 7. Illustration of a coronavirus particle [8].

Asper *et al.*, as seen in **Figure 8**, proved that the nanocellulose-based filters could filter 50-nm gold nanoparticles and 100-nm latex beads. They came to the conclusion that endogenous rodent retroviruses also retrovirus-like particles may be eliminated in the process of production of recombinant proteins using the shown filter paper based on nanocellulose [69].

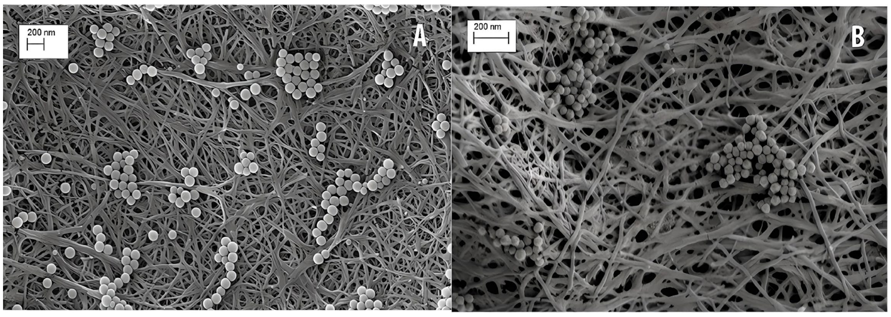

Figure 8. SEM images of 100 nm latex beads (A) and 50 nm Au nanoparticles (B). Retained on the nanocellulose filter paper [70].

4.2. Nanocellulose for Drug Delivery Applications

Cellulose has a proven track record of performance in medications and goods that have been accepted by the US Food and Drug Administration. Cellulose acetate (CA), for instance, has been effectively utilized in a number of medications of HIV, two antibiotics, five flavonoids, and a painkiller, to mention a few [71]. Additionally, formulations for oral medication administration have made use of hydroxypropyl methylcellulose. Controlling the rate of release of drug and achieving the proper concentration of drug are two important goals of employing cellulose as an excipient in medications. Because of its affinity for water, this natural polymer may also be cross-linked to create hydrogels. Furthermore, cellulose and its derivatives are safe for the human body to consume, and in the gastrointestinal system, some of the derivatives can be converted into natural metabolites by digestive enzymes. In recent years, there have been the introduction of a number of systems of drug delivery based on nanocellulose materials for a range of pharmaceutical purposes [2]. Trovatti *et al.* (2011) utilized bacterial nanocellulose membranes as platforms for lidocaine topical delivery. Greater than 90 percent of the total drug was on the loose in the first twenty minutes of in vitro drug release experiments conducted at 32°C in a buffer solution (pH 7.4) of phosphate. Three distinct a gel, BNC-lidocaine systems-BNC, and an aqueous solution were tested for therapeutic efficacy using human epidermis in vitro. In comparison to the additional two systems (aqueous solutions plus gels), it was discovered that the rate of penetration of lidocaine in the bacterial nanocellulose membranes was noticeably reduced [72]. BNC was examined as a possible medication delivery method for proteins with serum albumin in a different investigation by Psimadas *et al.* They discovered that compared to the original BNC samples, the freeze-dried bacterial nanocellulose samples had a reduced protein absorption. Lastly, Psimadas *et al.* demonstrated that albumin's biological stability was preserved throughout the materials processing procedure [73]. The idea of carriers for drug-delivery based on materials of nanocellulose was modified for amine-comprising medications by Dash and Ragauskas in 2012 [74]. In this work, γ aminobutyric acid, plus a spacer molecule, was grafted on CNCs using a process of periodate oxidation Schiff's base condensation. A linker known as syringyl alcohol was then employed as an aromatic releasable linker and connected to the targeted moiety in order to attain a gradual as well as fast release profile [2].

4.3. Nanocellulose for Wound Healing Applications

A topical use of cellulose materials, particularly bacterial nanocellulose (BNC), in wound healing is amongst their greatest well-known healing uses. Several research in the field of wound curative have demonstrated that BNC is a better option than traditional materials for wound-dressing. For topical use in wound curative, dressing products based on BNC including Bioprocess, XCell, and Biofill are now commercially obtainable [12]. There have already been reviews of the uses of materials based on BNC for restoration of skin-tissue elsewhere [2]. BNC membranes were utilized by Czaja *et al.* (2007) to cure patients who had severe second-degree scalds. According to the study, individuals whose scalds were coated with a membrane of bacterial nanocellulose saw a quicker rate of skin healing than those who got traditional wound dressings. According to Czaja *et al.*, never-dried bacterial nanocelluloses dramatically decreased wound pain, maintained a normal water balance, and demonstrated amazing conformability to a variety of body counters [64]. More recently, research on animals by Fu *et al.* (2013) also verified that BNC-based dressing materials have a reduced inflammatory response, a better healing effect, and quicker tissue regeneration [61]. Bacterial nanocellulose has been employed as a possible in vivo skin-tissue regeneration material to substitute traditional gauze bandages, according to a current study by Fu *et al.* (2012). In a further study, two distinct commercial dressings Vaseline gauze and Algisite M were compared with BNC wound dressing materials in a rat model [2]. In contrast to previous groups, the study demonstrated that animals dressed with BNC exhibited faster wound curative on day 14 with no signs of toxicity, confirming the effectiveness of bacterial nanocellulose dressing materials for therapeutic applications. Additionally, carboxymethylcellulose (CMC) may find application in materials for wound dressings. Using a rat model demonstrated that an in-situ cross-linked hydrogel created by cross-linking oxidized carboxymethylcellulose (OCMC) with carboxymethyl chitosan could cure second-degree burns at 14 days after wounding without causing any notable side effects. All things considered, BNCs and other nanocellulose materials make up a potential biopolymer for skin-tissue restoration applications [2].

Many pathophysiological processes, including tissue regeneration, repair as well as rebuilding, occur throughout the wound-healing process. A process known as angiogenesis involves the formation of a particular cell type (endothelial cells), is another significant biological event. Because newly formed vessels of blood enable the delivery of nutrients as well as oxygen to cells at the wound site, angiogenesis is a crucial factor in wound healing (**Figure 9**). Thermal source wounds provide a significant challenge for medical professionals, particularly because of the elevated danger of infections caused by bacteria. Infections can cause up to 75% of burn patients' morbidity and slow the healing of wounds. Furthermore, prolonged burn injuries to the skin may cause significant fluid loss and even patient death. Therefore, appropriate wound healing is essential to the survival of

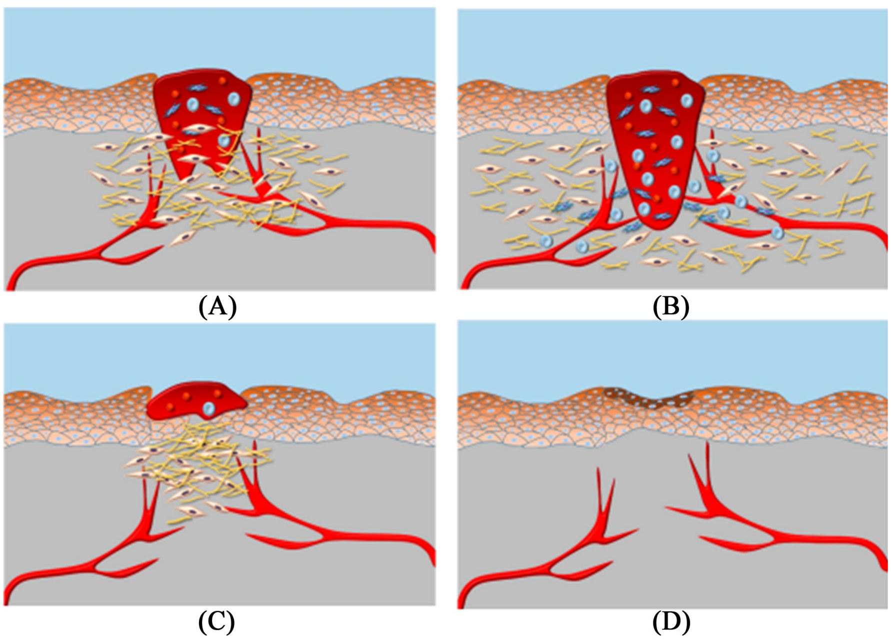

Figure 9. (A) The wound causes the formation of the clot (dark red area) and the recruitment of macrophages (blue) and neutrophils (round blue); (B) Fibroblasts (white) are also recruited to the wound site to fill it via collagen production (light brown); (C) Collagen and fibroblats rebuilt the tissue inducing endothelial cells proliferation and vessel generation; (D) Skin stem cells generate mature skin cells obtain the wound closing [3].

burn victims. In individuals receiving cancer therapies, wound healing is also crucial. Oncological therapy for these patients may reduce tissue vitality, which makes wound healing difficult. Lastly, individuals with comorbidities may also have difficulty mending their wounds, which may hinder the healing process [3].

4.4. Nanocellulose for Tissue Engineering Applications

Tissue engineering is another field with novel and intriguing potential applications for nanocellulose materials [75]. An excellent material contender for a range of tissue engineering utilizations is called cellulose [76]. Pre-present materials that were first created for various uses were used to create the vascular grafts, first dialysis membranes, complete hip replacements, and intraocular implants [77]. Despite the diversity of biomaterials research, the creation of scaffolds for tissue engineering which need dynamic interactions between live cells is where the necessity for careful materials engineering is most evident. The goal of tissue engineering is to repair impaired tissue in a number of means using live cells. Numerous efforts have been made to create scaffolds for tissue engineering for a broad range of organs and tissue types. Mesenchymal stem cells have been utilized to create bone using polycaprolactone/hydroxyapatite composite nanofibers [78], and the larynx has been tissue-engineered utilizing decellularized human tissue [79]. Although bio-nanocomposite materials containing hydroxyapatite (HA) have been created using a variety of cellulose species, BNC appears to be the utmost favorable material for possible tissue engineering, primarily due to its high porosity and little cytotoxicity. Consequently, bacterial nanocellulose utilized in scaffolds for tissue engineering, has been used in the bulk of recent research for applications in tissue engineering. Researchers Watanabe *et al.* (1993) [76] looked into BNC's biocompatibility in cell cultures. This work used BNC generated by *Acetobacter aceti* to create a novel mammalian cell culture medium. The authors of this study demonstrated that a BNC membrane bathed in serum was a useful substrate for tissue engineering.

4.5. Soft-Tissue Implants and Cartilage Replacements

The mechanical, chemical, surface chemistry, and pharmacological characteristics of the implant should all be compatible with the host tissues. As cellulose interacts with surrounding media, including water, the fibrillar network of nanocellulose materials, as bacterial nanocellulose, gives the material excellent tensile mechanical capabilities and a hydrogel-like behaviour [64]. Furthermore, BNC in particular has been demonstrated to be biocompatible and nondegradable under physiological circumstances [80]. Unlike their degradable competitors, non-degradable biomaterials offer long-term chemical stability and robust mechanical qualities. BNC is an intriguing biomaterial option for pharmacological and biomedical applications, such as blood vascular, [81], meniscus, [82], as well as articular cartilage tissue engineering, because of all these important properties [64]. Another essential component of scaffold applications is interconnected porosity, which enables chondrocytes to enter and move across the biomaterial. In recent years, a number of methods have effectively produced bacterial nanocellulose scaffolds with high hole sizes, permitting the seeded cells to permeate throughout the scaffold, despite the fact that bacterial nanocellulose is believed to be impermeable by cells because the pore size are too small [2].

4.6. Nanocellulose for Cardiovascular Applications

BNC-based implants have been created by a number of research teams and adhere to standard sterilization procedures, endothelization, cell ingrowth, surgical handling, and blood and tissue compatibility [83]. In a series of studies, Klemm and colleagues [84] created prototypes of BNC tubes with varying diameters for use in artery grafting applications (**Figure 10(A)**). According to preliminary research, BNC tubes may be sterilized using normal methods and have excellent surgical handling qualities. The tubes of BNC were effectively employed to substitute carotid arteries in a continuation in vivo investigation involving pigs, sheep, also rats. In cardiovascular tissue replacement applications, it's critical to make sure the surrounding tissues and implanted device have a good mechanical fit. One of the main causes of eventual graft failure also intimal hyperplasia in the presently utilized cardiovascular graft substitutes has been identified as a mechanical mismatch between the surrounding native tissue and the man-made compliant grafts prepared by elastic polymers, for instance expanded polytetrafluoroethylene and polyester (Dacron) [2]. Anisotropic nanocelluloses based on BNC and PVA were described by Millon *et al.* (2008) [85] as a solution to this issue. These NCs have a controllable degree of anisotropy and a wide range of mechanical characteristics, making them appropriate for possible replacement of cardiovascular tissue. Within the physiological range, the mechanical characteristics of the pig aorta and the PVA-BNC nanocellulose materials were almost identical. More recently, Azevedo *et al.* (2013) [86] created hollow tubes with small diameter with a compliance that was nearly identical to human coronary arteries using blends of cellulose and chitosan. By simply altering the proportions of each component, one may adjust the mechanical characteristics of the chitosan/cellulose mixes. Additionally, as a possible man-made biocompatible option for coronary artery bypass graft utilizations, these synthetic tubes based on biopolymer demonstrated cell compatibility characteristics which are encouraging for additional research [2].

4.7. Nanocellulose for Bone Regeneration Applications

Given the rising life expectancy and the prevalence of bone-loss-causing illnesses such infections, tumors, also injuries, technology for bone graft optimization is critical. Nanocellulose, among other materials, is becoming a desirable option for the creation of innovative and successful bone grafting methods. Microparticles for bone regeneration have also been made using carboxymethyl cellulose (CMC) [87]. Microparticles can be employed as delivery systems for bioactive substances as well as a short-term support for cell adhesion and proliferation. Through ionic crosslinking, CMC has been joined with the zirconium (Zr) aqueous ion complex, and then complexed with chitosan (CS). The authors believe that carboxymethyl cellulose (CMC) is especially suitable for attaching the positively charged atoms of zirconium because of the negative charge on the carboxyl group and its biocompatibility. Additionally, Zr in culture enhances human osteoblast development and proliferation [88]. Because it can be easily chemically modified to produce molecules with the necessary chemical-physical properties, CS, a great molecular weight polysaccharide of natural source, is frequently utilized as a transfer medium [89].

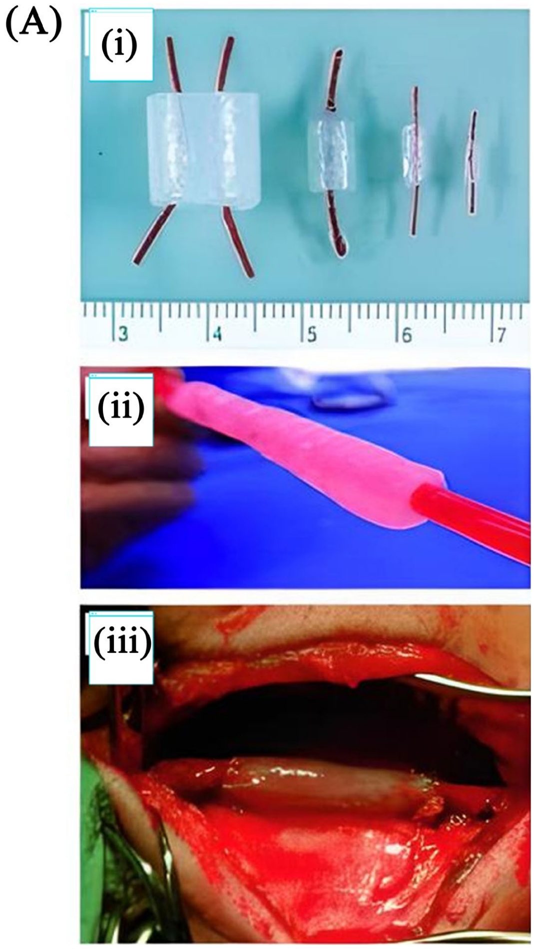

Figure 10. (A) Cardiovascular applications of BNC-based materials. (i) BNC tubes for arterial grafting applications. (ii) Long BNC tube used as a blood-vessel implant. (iii) BNC tube as a long-segment vascular graft for the right carotid artery of a sheep [2].

4.8. Nanocellulose for Dental Applications

The materials containing cellulose employed in the majority of dental treatments must last as long as feasible at the application site, in difference to the disciplines of wound curative and regeneration of bone. Due to its considerable versatility in clinical settings, glass ionomer cement (GIC), which is widely used in curative dentistry, has continuously increased in quality. Nanofiber cellulose (NFC) is being used as a strengthening factor in dental restorative material through the development of new GIC formulations. Silva *et al.* (2016) [90] recently used NFC from eucalyptus pulp to modify traditional GIC. A network of long fibres with regular diameter and random dispersion within the matrix was visible on the surface of the glass ionomer cement-nanofibrillated cellulose 0.4 percent (G04). Furthermore, it was discovered that the inclusion of NFC significantly improved every mechanical property of the material that was produced. The potential of ramie fibre as a strengthening ingredient for resin based on denture has been the subject of primary research. Ramie, which also referred to as "china grass" and the best fibres, are taken from the phloem tissue of plant. It was discovered that adding natural fibres improved the mechanical qualities even when the cellulose fibres were not nanoscale. Compared to plain resin, this modified denture composite generally had a greater flexural modulus; nevertheless, because of the poor interfacial adhesion, the flexural strength decreased [3].

5. Conclusions

With exceptional qualities, nanocellulose one of the utmost favorable green materials of our time has shown numerous uses in a variety of industries, from common one to high-tech biomedical. The enormous potential of nanocellulose in the medical domain is highlighted in this review. NCs, for example, have shown remarkable qualities which can be utilized in cartilage or bone tissue engineering or the formation of complex constructs with inter-connected macropores and vascular-like structures. NCs have shown great promise as a constituent in a diversity of formulations for applications in tissue engineering. Additionally, NCs appear to be the best option for sophisticated wound care techniques, such as encapsulating antimicrobial agents for wounds caused by bacteria or using them as strengthening material in the creation of smart dressings with sensors that react to particular variations in the wound environment and address particular pathological conditions at the level of molecule. Numerous biomedical and biotechnological applications, such as tissue engineering, dental and cardiovascular applications, drug delivery, antibacterial, wound coverings, medical implants, and bone regeneration, hold great promise for cellulose materials. Bacterial nanocellulose, is one of the numerous possible nanocellulose materials that has been thoroughly studied and shown promise in a variety of biomedical applications, ranging from scaffoldings for tissue engineering to topical wound dressings. According to preliminary research, Bacterial nanocelluloses are superior biomaterials for tissue engineering when compared to other natural polymers; this is probably because of their compatibility as well as endurance.

The cost-effectiveness of nanocellulose production and scalability of nanocellulose are critical factors limiting its widespread adoption. Chemical methods for the production of nanocellulose can result in the degradation of cellulose and the introduction of potentially cytotoxic byproducts. Even while these techniques may produce vast amounts of nanocellulose, they frequently have significant raise environmental issues due to waste formation and energy use. Variations in production methods can lead to inconsistencies in nanocellulose properties, making it challenging to achieve reproducible results. To guarantee constant quality control throughout the production process, sophisticated characterization techniques are required. Controlling the degree and type of modification to achieve desired properties while maintaining biocompatibility is a significant challenge. Some modification methods may compromise the inherent biodegradability of nanocellulose which is a critical requirement for many biomedical applications. Therefore, the development of environmentally friendly and biocompatible modification methods is crucial for the widespread adoption of functionalized nanocellulose in the biomedical field. The remarkable interest in the development of nanocelluloses is predicted to remain to grow. To meet this demand, it is essential to update also overcome obstacles like identifying production processes that are low in consumption of energy, cheap, and have a higher production capacity.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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