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Review Paper

Advancements in Functionalized Nanocellulose and Its Composites for Biomedical Applications

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Abstract: Functionalized nanocellulose is an emerging nanomaterial with great potential for biomedical applications. Its unique properties, including biocompatibility, biodegradability, and high mechanical strength, make it an attractive material for use in the biomedical field. The functionalization of nanocellulose is a critical aspect of its application in biomedical sectors as it enables the modification of its properties to meet specific requirements. This manuscript aims to review recent advancements in the field of functionalized nanocellulose and its composites for biomedical applications. The review focuses on the functionalization of nanocellulose, including methods of modification, as well as the potential applications of functionalized nanocellulose in controlled drug delivery, tissue engineering, wound healing and antimicrobial materials. Additionally, the current state of research on functionalized nanocellulose composites and their potential for use in biomedical sectors is discussed. This review highlights the importance of functionalized nanocellulose in the development of novel biomedical materials, and aims to provide insight into the current state of research on its potential applications in the biomedical field.

Keywords: Nanocellulose; Biomedical; Functionalization; Applications

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1. Introduction

The biomedical sector is expected to continue to play a major role in shaping the future of healthcare, improving patient outcomes, and advancing the state of medicine. Research and development (R&D) play a crucial role in advancing the biomedical sector. Biomedical R&D is responsible for the discovery and development of new treatments, drugs, diagnostic tools, and medical technologies that improve human health and well-being [1]. These advancements help in reducing the burden of diseases, improving patient outcomes, and extending human lifespan. Additionally, R&D also plays a significant role in the development of new knowledge and understanding of the underlying mechanisms of diseases and biological systems, which is essential for developing new and more effective treatments.

In recent years, biomaterials are emerging as an important area in medical science, with a growing number of research studies focused on developing new and innovative materials for use in medical applications [2,3]. The development of new biomaterials has the potential to address a wide range of medical needs, from improving patient outcomes to advancing medical technologies. Some of the key areas where biomaterials are emerging include drug delivery, tissue engineering, wound healing, and implantable devices [4–6]. For example, researchers are developing new and improved materials for drug delivery systems, such as nanomaterials and polymeric materials, that can help to increase the efficacy of drugs and improve patient outcomes. Similarly, the use of biomaterials in tissue engineering is helping to advance regenerative medicine and create new approaches for treating damaged or diseased tissues. Biomaterials are also being used to develop wound dressings and bandages that can promote healing and reduce the risk of infection.

However, despite the many successes that have been achieved in the field of biomaterials, there are still many challenges that need to be addressed. One of the main challenges is to develop biomaterials that are biocompatible and can be safely used in the human body without causing adverse reactions or complications. This is particularly important for materials that will be used in implantable devices or in other applications where they will be in contact with human tissues for extended periods of time. In addition, biomaterials need to be designed to have specific properties that are appropriate for the intended application. For example, a biomaterial used for drug delivery needs to be able to release the drug at the appropriate rate and in the appropriate location in the body. Similarly, a biomaterial used for tissue engineering needs to have the appropriate mechanical properties and be able to support the growth and differentiation of cells.

Nanocellulose is one of the biomaterials that has been attracting increasing attention for its potential applications in various fields such as adsorption [1], sensors [2], energy [3], explosive materials [4], and biomedical fields. Besides that, as is seen in Fig. 1, a search was done on lens.org using the keyword ‘Nanocellulose applications in biomedical’ and it was found that manuscripts focusing on this area have increased in recent years. Thus, this shows that research on the applications of nanocellulose in biomedical continues to gain much interest among scientist in this decade. Nanocellulose is a biodegradable and biocompatible material made from cellulose, which is the most abundant polymer on earth. Research on nanomaterials has received much attention in recent years due to their unique and promising properties. Nanomaterials are materials with structures and properties that are determined by their size and shape at the nanoscale (typically 1 to 100 nanometers) [7–9]. One of the unique properties of nanocellulose is its high strength and stiffness, making it a promising candidate for use in medical implants and scaffolds. In addition, nanocellulose also has excellent hydrophilic properties, which make it suitable for use in wound dressings and drug delivery systems. Another advantage of nanocellulose is its biodegradability, which means that it can be safely degraded by the body after its use, reducing the risk of long-term complications. Additionally, nanocellulose is non-toxic, which further enhances its potential for use in biomedical applications.

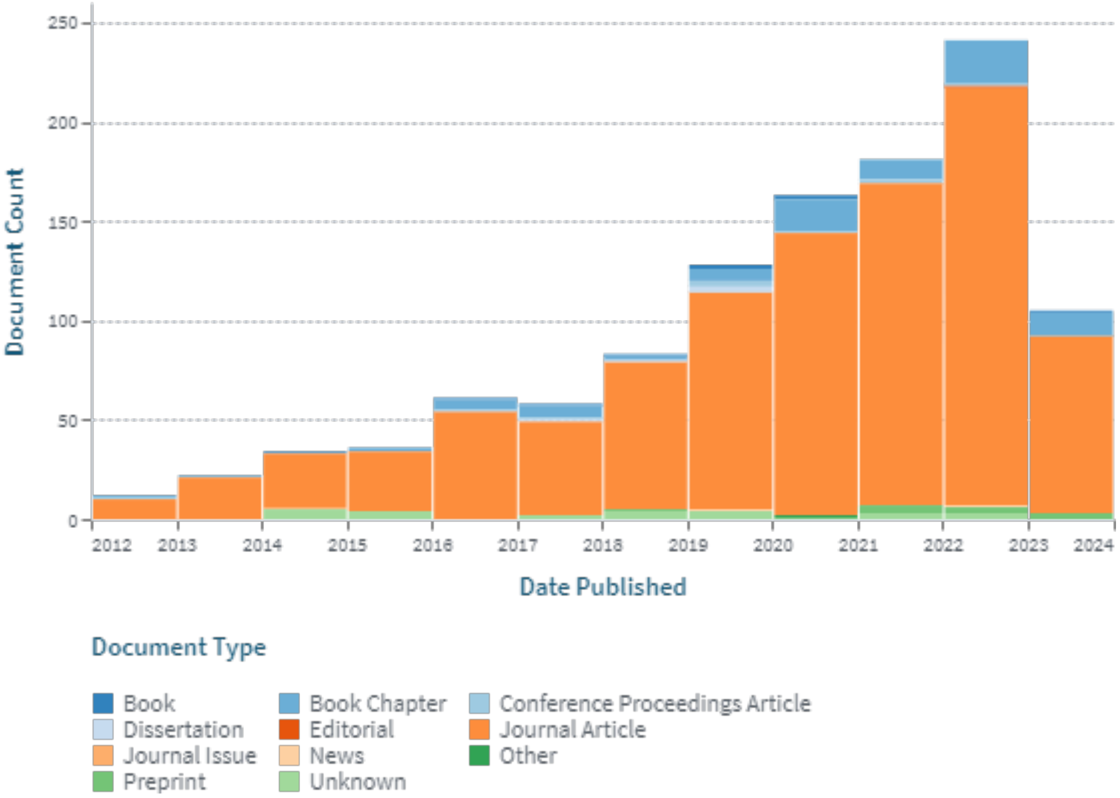

Figure 1. Scholarly articles related to nanocellulose applications in biomedical

In addition to the unique properties of nanocellulose, another key area of research in the field of biomedical applications is the functionalization of nanocellulose [10–12]. Functionalization is the process of modifying the surface of nanocellulose to impart specific properties, such as enhanced biocompatibility, improved drug loading and release, and targeted delivery to specific cells or tissues. The functionalization of nanocellulose can improve its properties, such as enhancing its biocompatibility, modifying its surface properties, and providing targeted drug delivery. The various functionalization methods that have been developed include chemical modification, surface modification, and the incorporation of other biomaterials.

Therefore, in this review, we have explored the potential of nanocellulose as a promising biomaterial for biomedical applications. We have discussed the current research findings on the use of nanocellulose in biomedical applications and the ongoing efforts to functionalize it for specific applications.

2. Nanocellulose: Classification and Properties

Nanocellulose is a type of cellulose that has been processed into nano-sized fibers or particles. It is obtained from natural sources such as wood, cotton, or bacteria, which are broken down using mechanical, chemical, or enzymatic methods [5]. The resulting material is composed of cellulose nanofibrils (CNF), cellulose nanocrystals (CNC), or bacterial nanocellulose (BNC), each with their unique properties and applications [6].

CNF is obtained from wood pulp, which is mechanically treated to separate the cellulose fibers. The fibers are then subjected to high-pressure homogenization or microfluidization to break them down into nanofibrils. CNF have a high aspect ratio, with lengths up to several micrometers and diameters in the nanometer range. They are highly crystalline and have excellent mechanical properties, including high strength, stiffness, and toughness. CNF also have a high surface area, which makes them useful for applications such as reinforcement in composites, paper coatings, and adhesives.

CNC is obtained from acid hydrolysis of cellulose fibers. The hydrolysis process removes amorphous cellulose, leaving behind highly crystalline CNC with high aspect ratios and diameters in the range of a few nanometers. CNC have excellent mechanical properties, high surface area, and unique optical and electrical properties, which make them useful for applications such as reinforcement in composites, coatings, and films, as well as in electronic devices and sensors.

BNC is produced by certain bacteria, such as *Gluconacetobacter xylinus*, which secrete cellulose fibers as part of their extracellular matrix. BNC has a high degree of purity, with a high crystallinity index, high strength, and high water-holding capacity. BNC also has a unique three-dimensional structure, which makes it useful for applications such as wound dressings, tissue engineering, and medical implants. Table 1 summarizes the properties of different types of nanocellulose.

Table 1. Properties of nanocellulose for biomedical applications

Type of nanocellulose	**Size range (nm)**	**Aspect ratio**	**Surface area (m2/g)**	**Mechanical properties**	**Biocompatibility**
Cellulose nanocrystals	5-50	10-100	50-200	High stiffness and strength, high Young's modulus	Generally biocompatible, can cause inflammation at high concentrations
Cellulose nanofibrils	10-1000	10-1000	30-200	High tensile strength, low stiffness and Young's modulus	Generally biocompatible
Bacterial cellulose	20-1000	>1000	30-60	High purity, high water-holding capacity, high tensile strength	Generally biocompatible, can cause inflammation at high concentrations

Overall, nanocellulose has several attractive properties for biomedical applications, including high biocompatibility, biodegradability, and low toxicity. It can also be functionalized to enhance its properties, such as through surface modification or chemical derivatization, which can improve its solubility, reactivity, and compatibility with other materials. The next section will discuss the functionalization of nanocellulose for biomedical applications.

3. Functionalization of Nanocellulose

Functionalization is a process of modifying the surface of nanocellulose to impart specific properties or to facilitate the attachment of other functional groups [7]. Functionalization can be achieved by several methods, including physical adsorption, covalent binding, and surface modification. The choice of functionalization method depends on the desired properties of the nanocellulose and the intended application.

3.1 Physical Adsorption

Physical adsorption is a simple and effective method of functionalizing nanocellulose. In this method, functional molecules are adsorbed onto the surface of nanocellulose through non-covalent interactions, such as Van der Waals forces, hydrogen bonding, and electrostatic interactions. Physical adsorption is a reversible process, which means that the functional molecules can be easily desorbed from the surface of nanocellulose. Therefore, physical adsorption is suitable for applications where the functional molecules need to be released gradually over time, such as in drug delivery systems.

3.2 Covalent Binding

Covalent binding is a more permanent and stable method of functionalizing materials [8]. In this method, functional groups are chemically bonded to the surface of nanocellulose through covalent bonds. Covalent binding is a more complex process compared to physical adsorption, and it requires the use of coupling agents, such as carbodiimides and epoxides. Covalent binding is suitable for applications where a high degree of stability and permanence is required, such as in tissue engineering and implantable devices. Esterification, silylation, amination, oxidation, sulfonation, carboxymethylation, polymer grafting, and other chemical modification procedures are commonly used to establish covalent connections with reactive groups on the surface of nanocellulose.

3.3 Surface Modification

Surface modification is a method of functionalizing nanocellulose by modifying the surface chemistry of the material [9]. Surface modification can be achieved by several methods, including plasma treatment, chemical etching, and grafting. Surface modification can improve the adhesion of nanocellulose to other materials, such as polymers and metals, and it can also impart specific properties, such as hydrophobicity and antimicrobial activity. Surface modification is suitable for applications where the surface properties of nanocellulose need to be modified to achieve specific functionalities. Table 2 shows summary of common surface functionalization methods for nanocellulose.

Table 2. Comparison of Functionalization Methods for Nanocellulose

Functionalization Method	Advantages	Disadvantages
Physical Adsorption	Simple and reversible process, suitable for controlled release applications.	Limited stability and permanence.
Covalent Binding	Permanent and stable functionalization, suitable for tissue engineering and implantable devices.	Complex process, requires the use of coupling agents.
Surface Modification	Can modify surface properties to achieve specific functionalities, suitable for	May alter the structure and properties of nanocellulose,

		improving adhesion and imparting specific properties.	requires specialized equipment.

4. Functionalized Nanocellulose and its Application in Biomedical

In this section, we will explore some of the current and potential applications of functionalized nanocellulose in biomedical fields. Nanocellulose has gained significant attention in recent years due to its unique properties, such as high strength and stiffness, biocompatibility, and biodegradability, which make it an attractive material for use in various biomedical applications. Additionally, functionalization of nanocellulose can further enhance its properties and enable it to be tailored for specific applications. In this section, we will discuss some of the current and potential applications of functionalized nanocellulose, including drug delivery systems, wound healing, tissue engineering, and diagnostic imaging.

4.1 Drug Delivery System

Functionalized nanocellulose has shown potential as a drug delivery system due to its unique properties, such as its high surface area, high mechanical strength, and biocompatibility. The functionalization of nanocellulose can enhance its drug loading and release capacity, improve its targeting ability, and increase its stability in biological fluids [10]. Here are some examples of how functionalized nanocellulose is being used in drug delivery systems:

Targeted drug delivery

Researchers are using functionalized nanocellulose to create targeted drug delivery systems. By functionalizing nanocellulose with targeting molecules such as antibodies, peptides, or aptamers, drug molecules can be specifically delivered to the desired site of action, reducing the risk of off-target effects and improving drug efficacy.

Controlled drug release

Functionalized nanocellulose can be used to control the release of drugs in a controlled manner. By modifying the surface of nanocellulose with pH-sensitive or temperature-sensitive polymers, drug release can be triggered in response to specific stimuli such as changes in pH or temperature.

Improved solubility and stability

Functionalized nanocellulose can improve the solubility and stability of poorly soluble drugs. By coating the drug molecules with nanocellulose, drug solubility can be increased, while stability can be improved by protecting the drug molecules from degradation.

Several studies have reported on the efficacy of functionalized nanocellulose in drug delivery system. Recently, Wong et al. (2021)[11] have strategized the modification of the primary and secondary hydroxyl groups on the CNC by introduced amine and iodine group substitution. The study functionalized nanocellulose with amine groups and radiometal loaded-chelates or fluorescent dyes to create water-soluble and biocompatible fibrillar nanoplatforms for gene, drug, and radionuclide delivery. The nanocellulose was found to have a length of 162.4 ± 16.3 nm, diameter of 11.2 ± 1.52 nm, and aspect ratio of 16.4 ± 1.94 per particle. In vivo studies showed that more than 50% of the injected functionalized CNC was excreted in the urine within 1 hour, and tissue distribution revealed accumulation in the kidneys, liver, and spleen. The functionalized nanocellulose shows potential as a drug delivery platform for the kidneys.

Besides that, Tang et al. (2018)[12] developed a colon-targeted drug release system using maleic anhydride CNC (MCNC) conjugated with a model drug (tosufloxacintosilate) and L-leucine as a spacer molecule. The MCNC showed satisfactory drug loading and high encapsulation efficiency. FTIR and XPS spectra confirmed the successful linking of L-leucine to MCNC and amidation reaction between drug and A-MCNC. In vitro studies and fluorescence detection showed that the drug conjugates could release about 72.55% of the drug loaded in the simulated colon fluid with enzyme lysozyme after 30 hours, indicating excellent behavior for colon-targeted release. The study highlights the potential of cellulose nanocrystals as carriers in colon-specific drug delivery systems.

4.2 Wound Healing

Another important application of functionalized nanocellulose in the biomedical field is in wound healing. The unique properties of nanocellulose, such as its high surface area, biocompatibility, and ability to form hydrogels, make it an ideal candidate for wound healing applications. One way that functionalized nanocellulose can be used in wound healing is through the creation of dressings or scaffolds. These materials can be used to promote cell proliferation and tissue regeneration, while also providing a barrier to prevent infection.

Several studies have demonstrated the effectiveness of nanocellulose-based wound dressings in promoting wound healing. For example, Patel et al. (2022)[13] synthesized an injectable and adhesive hydrogel made of spherical CNC (s-CNC) and carboxymethyl chitosan for rapid skin regeneration. The s-CNC demonstrated improved cellular activity compared to CNC. The hydrogels showed adhesive and injectability properties and were molded into desired shapes. Additionally, the s-CNC added hydrogels exhibited enhanced conductivity and antibacterial potential. The hydrogel scaffolds were examined in a rat wound healing model, and the composite scaffolds demonstrated improved skin regeneration potential.

Moreover, Liu et al. (2021)[14] designed of bioactive CNF scaffolds with controlled release of basic fibroblast growth factors (bFGFs) for wound healing applications. The polyion complex interaction between positively charged bFGFs and negatively charged CNF enables the storage of bFGFs in a readily available form from where it is slowly released and potentially protected from denaturation. The release profile of bFGFs can be tailored by tuning CNF surface chemistry and in situ deconstruction of the scaffolds. The scaffolds facilitate cell proliferation, even with a small amount of bFGFs loaded, and the enzymatic deconstruction of the CNF network increases the bFGFs bioavailability and promotes cell proliferation.

4.3 Tissue Engineering

Tissue engineering is another promising area where functionalized nanocellulose can be used. Nanocellulose has been found to possess unique properties that can be utilized to create various tissue engineering scaffolds. It can be used for cell adhesion, proliferation, and differentiation to promote tissue regeneration.

Functionalized nanocellulose can be used to create scaffolds with different shapes and sizes, ranging from 2D films to 3D porous structures. The nanocellulose scaffolds can be functionalized with various biomolecules, such as growth factors, peptides, and enzymes, to enhance their biological activity and promote tissue regeneration. Moreover, nanocellulose scaffolds have been reported to possess good mechanical properties, biocompatibility, and biodegradability, which makes them suitable for tissue engineering applications. In addition, the porous structure of nanocellulose scaffolds allows for good nutrient and oxygen transport, which is essential for cell growth and tissue regeneration.

Recently, Rashad et al. (2023)[15] exploring the effects of aldehyde groups on the surface of TEMPO-oxidized CNF (TO-CNF) on rat mesenchymal stem/stromal cells (MSCs) (Fig. 2). The authors replaced the aldehyde groups on the surface of TO-CNF with either carboxyl groups or primary alcohols with terminal hydroxyl groups. They then assessed the effect of these modifications on cell viability, spreading, alkaline phosphatase activity, and biomineralization. The results demonstrated that all nanocellulose biomaterials supported excellent cell viability, with more proteins adsorbed from cell culture media on all CNF surfaces compared to BNC. Interestingly, the TO-R-CNF samples, which had no aldehyde groups, showed better cell spreading than BNC and comparable results to polystyrene tissue culture plates (TCP). TO-R-CNF also stimulated cells in osteogenic medium to have higher alkaline phosphatase activity and to form more biomineralization than TCP and TO-CNF groups. Overall, these findings suggest that the presence of aldehyde groups on the surface of TO-CNF might have little or no effect on the attachment, proliferation, and osteogenic differentiation of MSCs.

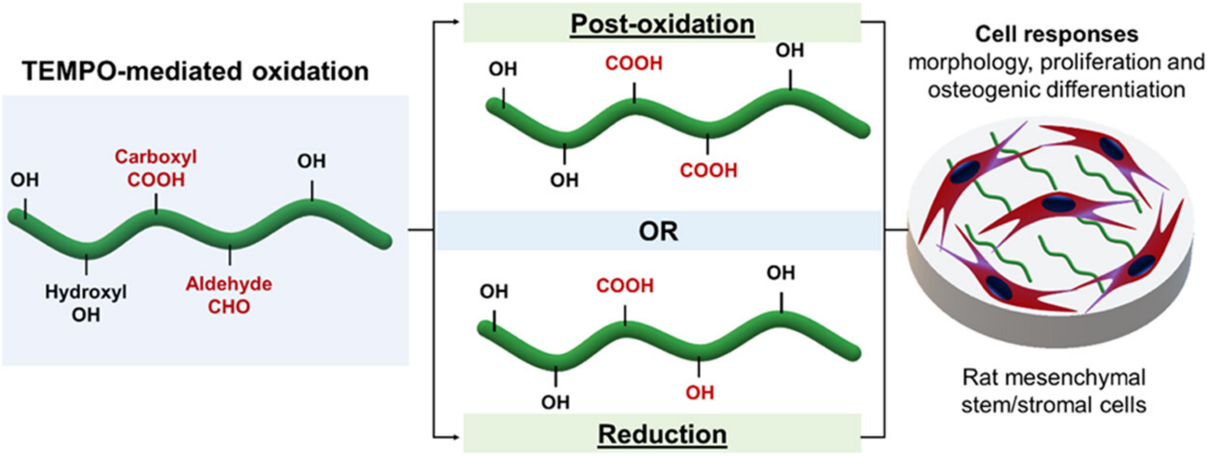

Figure 2. Development of TEMPO-oxidized CNF (TO-CNF)

4.4 Antimicrobial Materials

Antimicrobial materials are another application of functionalized nanocellulose in biomedical fields. The unique properties of nanocellulose make it an excellent candidate for designing antimicrobial materials. Nanocellulose-based materials can act as a carrier for antimicrobial agents and can be used for various biomedical applications, such as wound dressings, surgical masks, and filters [16].

Several studies have demonstrated the effectiveness of nanocellulose-based materials as antimicrobial agents. Bansal et al. (2021)[17] used CNF modified with quaternary ammonium salts (QNFC) to create an antimicrobial material that can effectively kill various types of bacteria. The fibers exhibited strong antimicrobial activity, with a maximum activity of 94.73% and 99.86% against *Escherichia coli* and *Staphylococcus aureus*, respectively, and the activity was sustained for up to six months. Another study by Errokh et al. (2019)[18] focused on functionalizing CNF with silver (Ag) nanoparticles (NPs) through Tollens' reaction to create Cel-Ag hybrid nanofibrils (Fig. 2). They found that the Cel-Ag nanofibrils had good bactericidal properties against both Gram+ and

Gram− bacteria, but the presence of Ag NPs did not appear to affect the reinforcing potential of the nanocellulose. Moreover, the amount of Ag that leached out from the films was below the permissible limit of 12 ppb. Authors suggested that the Cel-Ag nanofiller has great potential in creating active packaging films, coatings, and adhesives with enhanced antibacterial activity.

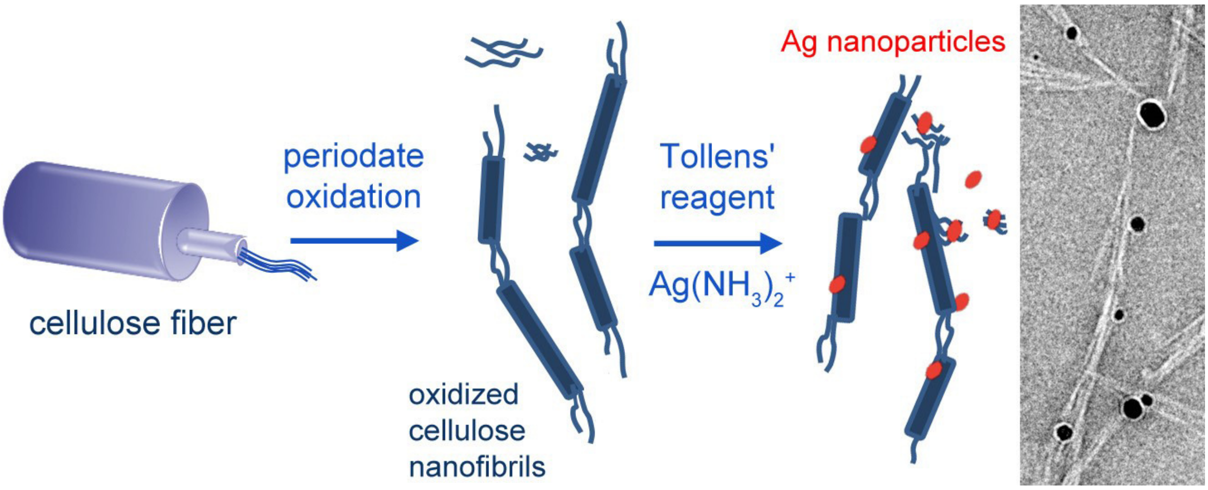

Figure 2. Functionalization of CNF with silver (Ag) nanoparticles (NPs) through Tollens' reaction to create Cel-Ag hybrid nanofibrils

5. Challenges and Future Recommendations

Despite the significant progress made in the functionalization and biomedical applications of nanocellulose, several challenges still need to be addressed. One of the major challenges is the lack of standardization in the characterization of nanocellulose, which affects the reproducibility of the results obtained from different studies. Therefore, there is a need for standardization of the methods used to characterize nanocellulose in order to ensure consistency and reproducibility of the results.

Another challenge is the biocompatibility and toxicity of functionalized nanocellulose. Although nanocellulose has been shown to be biocompatible, the effect of functionalization on its toxicity and biocompatibility is not well understood. Hence, it is crucial to investigate the long-term effects of functionalized nanocellulose in vivo to ensure its safety for biomedical applications.

Moreover, the cost of production of nanocellulose is relatively high, which limits its large-scale commercialization. Therefore, there is a need to develop cost-effective and scalable production methods for nanocellulose to enable its widespread use in various applications.

In terms of future perspectives, the potential of functionalized nanocellulose in biomedical applications is vast and promising. One of the future directions is the development of multifunctional nanocellulose-based materials that can simultaneously perform multiple functions such as drug delivery, wound healing, and tissue engineering. Additionally, the use of nanocellulose in combination with other materials such as polymers, metals, and ceramics can lead to the development of advanced materials with enhanced properties and functionalities.

Another promising area of future research is the use of nanocellulose in regenerative medicine. Nanocellulose-based scaffolds can be designed to mimic the natural extracellular matrix of tissues, providing a suitable environment for cell growth and differentiation. Furthermore, the use of nanocellulose in combination with stem cells can lead to the development of personalized regenerative therapies for various diseases.

In conclusion, the functionalization of nanocellulose has opened up new opportunities for its use in various biomedical applications. Although several challenges still need to be addressed, the potential of functionalized nanocellulose in biomedical applications is vast and promising. With further research and development, it is expected that nanocellulose-based materials will play a significant role in the future of regenerative medicine and other biomedical fields.

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