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PLANT-BASED CELLULOSE FIBER AS BIOMATERIALS FOR BIOMEDICAL APPLICATION: A SHORT REVIEW

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Abstract. *Cellulose is the most common polysaccharide that can be obtained from many resources. Plant-based cellulose (PC) is preferable due to its high renewability and natural availability. This inherent affluence naturally opens the door to new applications for this versatile material. PC provides various potential applications such as packaging, textile, and biomedical application. Currently, PC shows progress in its feasibility in biomedical applications because it fulfills the requirement of the characteristics of biomaterials such as biocompatible, biodegradable, anti-microbial, and enhancing tissue regeneration. Different morphological forms of PC include fiber, microfibril/nanofibril cellulose (MFCs/NFCs), and micro/nanocrystalline cellulose (MCCs/NCCs) adapted for different biomedical applications. This short review provides a general characteristic of plant-based cellulose (PC) and its potential to be applied in biomedical fields such as tissue engineering.*
Keywords*: Biomaterial; biomedical application; plant-based cellulose*

1. Introduction

Biomaterials have three main components: bioactivity, biocompatibility, and biomechanics [1]. According to this, cellulose fulfills the requirement of biomaterial because it is composed of a chain polysaccharide comprising glucose subunit polymers. Cellulose is an unbranched natural polymer composed of repeating glucose units to form a polysaccharide.

Cellulose as a natural fiber has advantages and disadvantages for its application. *Advantages*: In environmental aspects, cellulose is a renewable resource. Moreover, the energy required for cellulose production is relatively low compared to synthetic fibers. The disposal of cellulose doesn't need a complicated procedure as it is an organic product and does not pose bio-hazard and it can be disposed of by composting. In production aspects, cellulose is non-abrasive and great formability

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material. *Disadvantages*: The quality of cellulose as natural fiber is dependent on the plant source and the geographical location where the sources are cultivated. Moreover, cellulose also exhibits poor moisture resistance, impact strength, fire resistance, and adhesion in composite material. However, some effort has been carried out to improve the quality of cellulose for various utilization.

Cellulose can be obtained from plants, algae, oomycetes, and bacteria. However, cellulose derived from plants or plant-based cellulose (PC) is preferred due to its natural availability and renewability potential. In commercial applications, cellulose has been widely used in paper products, textiles, and packaging [2], [3]. In addition, it has shown some progress in how cellulose can be adopted as biomaterials for biomedical applications [4].

Plant-based cellulose (PC) can be extracted from a variety of plants, plant parts, and plant waste and PC is mainly found in plant cell walls. The content of cellulose varies in the different parts of the plant. The most common part along with the plant used for PC extraction is- *the roots* such as *Acalypha Indica* L; *the leaves* such as pineapple leaves, and banana leaf fiber; *the stems* such as sugarcane, and; *the fruits* such as soybean hulls [5]–[9]. The composition and structure of fiber derived from wood and plant are comparable, comprising biodegradable carbohydrate polymers such as cellulose, hemicellulose, and lignin [10].

Plant-based cellulose (PC) is processed and selected for different purposes based on its physical features, dimensions, and shapes, cellulose in the forms of fiber, microfibril/nanofibril celluloses (MFCs/NFCs), and micro/nanocrystalline celluloses (MCCs/NCCs). In the states of fiber, PC is typically found in three geometries; 1) strand fibers, 2) staple fibers, and 3) pulp fibers. These forms can be obtained through water retracting or pulping [10]. These processes will remove the lignin between cells and produce cellulose a few mm long [11].

Mechanically disintegrating cellulose fibers can obtain Microfibril/nanofibrils by passing through mechanical fibrillation, homogenizing process, or ultrafine grinding of cellulose and micro-fluidization [12]. These thin cellulose fibers often called cellulose microfiber (CMFs) or cellulose nanofibers (CNFs), have high crystallinity, excellent mechanical stiffness, and strength [13]. Their diameter is approximately 3 nm, and their micron-scale lengths have both crystalline and amorphous sections.

Microcrystalline celluloses (MCCs) or nanocrystalline cellulose (NCCs) can be extracted from CMFs through more complicated processes such as the combination of mechanical, chemical, and enzymatic treatments [14]. The primary differences between NCCs/MCCs and CNFs/CMFs are that CNFs/CMFs have both amorphous and crystalline cellulose domains with lengths ranging from a few micrometers to several micrometers, whereas NCCs/MCCs are highly crystalline. MCCs and NCCs are rigid rod-like particles made of cellulose chain segments in a nearly flawless crystalline form [15]. The NCC has a huge surface-to-volume ratio, a high modulus of elasticity, a high tensile strength, high stiffness, flexibility, and robust thermal, electrical, and optical characteristics [16]. The NCC can enhance bio-nanocomposite due to its versatility, adaptability, and biodegradability in the tissue to be utilized in biomedical applications such as implants for biomedical devices [17]. The diverse fiber hierarchy of the PC will offer materials with different characteristics, which are required for various biomedical applications.

2. Cellulose Isolation Sequences

Plant-based cellulose can be obtained in macro or nano size using chemical and mechanical methods. The importance of cellulose extraction into different forms is to get improved fiber properties such as high tensile strength and purity. There are several general sequencings for extracting cellulose from plant sources; 1) Preparation of clean raw fiber from the plant source, 2) Purification of fiber, 3) delivery of cellulose fibrils, 4) size reduction and drying process of cellulose fibrils, 5) cellulose characterization, further medication, and application purpose as shown in Figure 1.

The cleaned raw fibers from the plant are downsized into powder form by mechanical treatment through milling/grinding/cutting [18]. The powder form of threads has a uniform size with a millimeter size. After that, it will be chemically treated to get the finer fibers (pulp form) that increase the contact surface area between chemicals with active groups of cellulose fiber and even the rate of reaction for the purification process [19]. The pulp forms are washed in distilled or deionized water to remove dirt with constant stirring or to blend at a certain speed and then filtered to make the fibers disintegrate. Easy to split, the process can remove undesirable soluble components in water [20].

Plant-based celluloses (PCs) are rarely pure because they contain additional components that bond with cellulose, such as lignin and hemicelluloses [21]. Purification is required to eliminate parts other than cellulose since they decrease cellulose's crystallinity, thermal stability, and mechanical properties [22]. Cleansing will result in cellulose-rich or highly pure cellulose fibers, as well as cleaning and modifying the fiber surface. Because of the availability of ingredients such as NaOH/KOH, sodium chlorite, and acetic acid, the alkali-bleaching treatment is the most preferred traditional chemical treatment in the purification of cellulose fibers [23]. Individual threads of uniform size and even cellulose microfibrils can be obtained after this process.

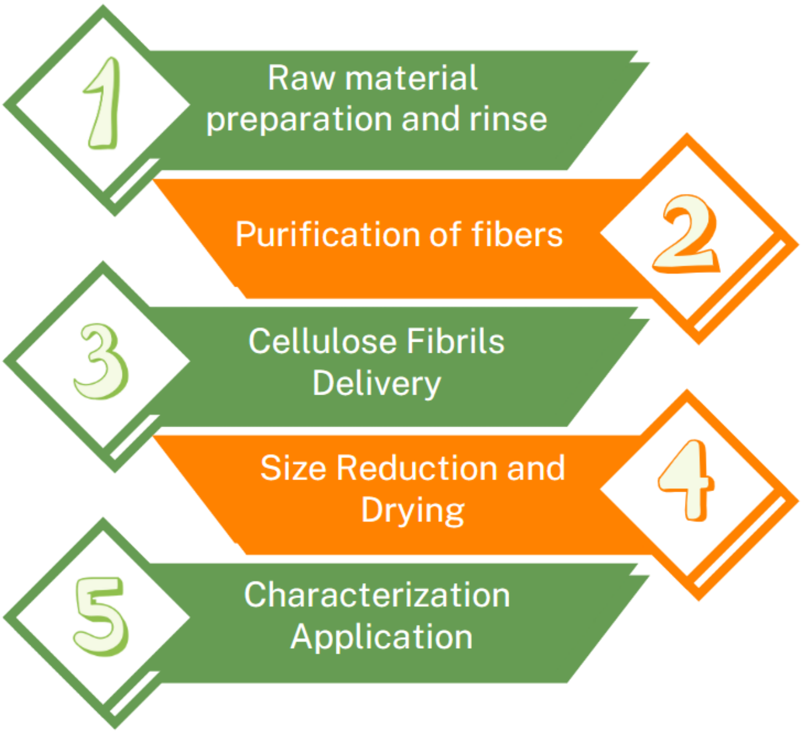

Figure 1. Schematic process flow of cellulose isolation

In cellulose fibrils, the crystalline structure can be seen as compact nanocrystals created by hydrogen bonding interactions between adjacent cellulose strands [18]. However, because the initial purification of the cellulosic components occurs primarily in amorphous areas, these cellulose crystals are bound together by disordered amorphous parts, which may compromise crystalline cellulose's mechanical and thermal characteristics [19]. Therefore, to efficiently retrieve high crystalline and purified cellulose nanocrystals, the unfavorable amorphous portions must be selectively eliminated using chemical and enzymatic treatments, with acid hydrolysis being the most often used method [21]. However, additional mechanical treatment can also be done if necessary [21]. After the treatment, cellulose fibrils from this process are usually stored in water suspension [22].

In the final stage, water is removed from the cellulose fibrils' suspension through several methods, including four methods (1) oven drying, (2) freeze drying, (3) supercritical drying (SCD), and (4) spray-drying (SD) as shown in Figure 2 [23]. The dried cellulose fibrils will be used for characterization such as Scanning Electron Microscopy (SEM), Fourier transform infrared (FTIR), and Raman spectroscopy for physiochemical assessment [24]–[26], further modification such as antimicrobial agent treatment [27], and possible application such as NCC based-composite [28].

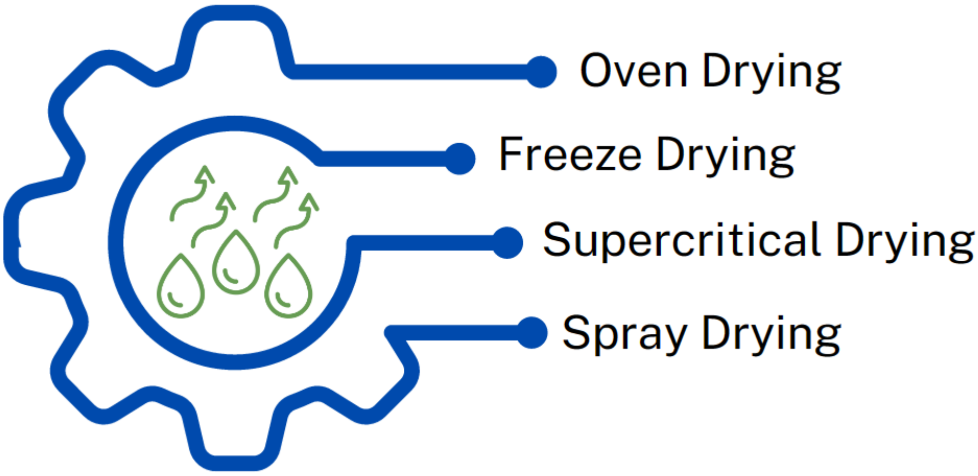

Figure 2. Schematic process flow of cellulose isolation

3. Characteristics of Cellulose as Biomaterials

All cellulose derived from different sources almost exhibits the same characteristics as biomaterials. The physicochemical properties of PC generally are shown below.

3.1. Mechanical Properties

Cellulose and its composites are being developed to develop high-performance mechanical and functional materials [29]. The high intrinsic stiffness and strength of cellulose crystals offer promising materials with outstanding mechanical properties when properly fabricated, making them a good candidate for biomedical applications requiring excellent mechanical performance. Table 1 shows the mechanical properties of several PC fibers and human tissues. The data showed that the range of Young's modulus of plant-based fiber appeared within 4–1128 GPa, while the tensile strength is within the range of 80–1627 MPa, and the elongation break is within 1.2-25%. These ranges may happen due to different impurities of different plant-based fibers [30]. After mechanical or chemical treatment, the impurities can be removed, increasing the PC's mechanical properties. As a result, the mechanical strength of PC appears tough, firm, and extendable, which can mimic the features of an ideal scaffold for tissue engineering [31].

3.2. Biocompatibility

Materials may cause a hazardous reaction in the short term or the long term when it is used in a host such cell, tissue, or organ. Therefore, biocompatible material is required for biomedical materials. Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application as illustrated in Figure 1. The biocompatible materials should exhibit non-toxic, non-thrombogenic, non-carcinogenic, non-antigenic, and non-mutagenic to exhibit an appropriate biological response [36]. Some study has shown that PC is biocompatible material as it can enhance the adherence of the cells and improve the extracellular matrix growth and growth of the cells [37].

Table 1. Comparison of plant-based fiber with human tissue [32]–[35]

	Tensile Strength (MPa)	Elongation break (%)	Young's Modulus (GPa)
Plant-based Fiber			
Flax	300–1500	1.3–10	24–80
Jute	200–800	1.16–8	10–55
Sisal	80–840	2–25	9–38
Kenaf	295–1191	3.5	2.86
Pineapple	170–1627	2.4	60-82
Banana	529–914	3	27–32
Oil palm (empty fruit)	130–248	9.7–14	3.58
Ramie	348–938	1.2–8	44–128
Hemp	310–900	1.6–6	30–70
Human Tissue			
Hard tissue (tooth and bone)	130–160	1–3	17–20
Skin	7.6	78	(0.42-0.85) x 10^{-3}
Tendon	53–150	9.4-12	1.5
Elastic cartilage	3	30	(0.85- 7.9) x 10^{-3}
Heart valves	0.45–2.6	10–15.3	
Aorta	0.07–1.1	77–81	

3.3. Biodegradability

The ability of organic materials to be biologically broken down by living organisms into their most basic components, such as water, carbon dioxide, methane, essential elements, and biomass, is known as biodegradability (Figure 3). Unfortunately, PC is difficult to degrade its insolubility characteristics in water and other common solvents [38]. However, its insolubility characteristics can be used depending on the specific conditions required for application, such as a long-term medical implant. Moreover, there are ongoing studies to develop innovative cellulose solvents with favorable properties to allow the usage of cellulose in biomedical applications [39].

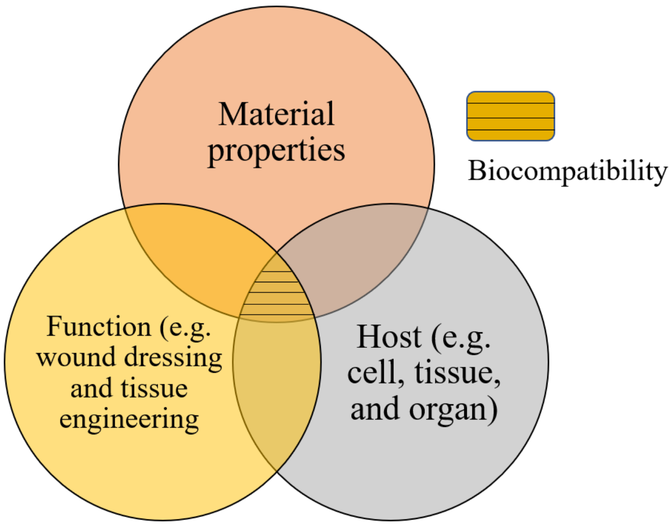

Figure 3. The consideration of biocompatibility for biomaterials on how material properties, host, and function interact with each other.

3.4. Oxygen Barrier

In tissue engineering, providing adequate or controlled oxygen supply to implanted tissue scaffolds and tissue is vital since oxygen diffusion acts as a signaling molecule for cell differentiation and growth [40]. In addition, the hypoxia state (low oxygen content) in wound healing will trigger angiogenesis to accelerate wound healing [41]. The compact structure formed by the nanofibrils in nano cellulose exhibits a strong oxygen barrier and has smaller and more uniform dimensions depending on the methods used to make it [42].

3.5. Anti-microbial

Antimicrobial property is crucial for biomaterials as it kills or slows the spread of unwanted microorganisms. The presence of bacteria in the tissue can accumulate toxic substances [43], such as endotoxin and exotoxin [44], and lead to infection [45]. The PC can serve as an antimicrobial biomaterial [46]. Some studies show that the incorporation of PC with other substances can provide anti-microbial materials such as *Uncaria gambir* - polyvinyl alcohol (PVA) composite [28] and nano cellulose conjugated lysozyme and allicin [27].

3.6. Cytotoxicity

Cytotoxicity is the toxicity caused by chemotherapeutic agents' action on living cells, such as cell death or damage [47]. Therefore, cytotoxicity tests are critical for biomaterials used in biomedical applications. For example, some studies have reported that the PC can interact with human cells without showing any significant cytotoxic effects after being tested *in vitro* models of co-cultured lung cells [48].

4. The Potential of Plant-based Cellulose in biomedical Applications

Figure 4 illustrates the potential of The PC to utilize as material in biomedical applications. This section discusses some of the applications including wound healing, bone tissue engineering, anti-microbial, and implant material.

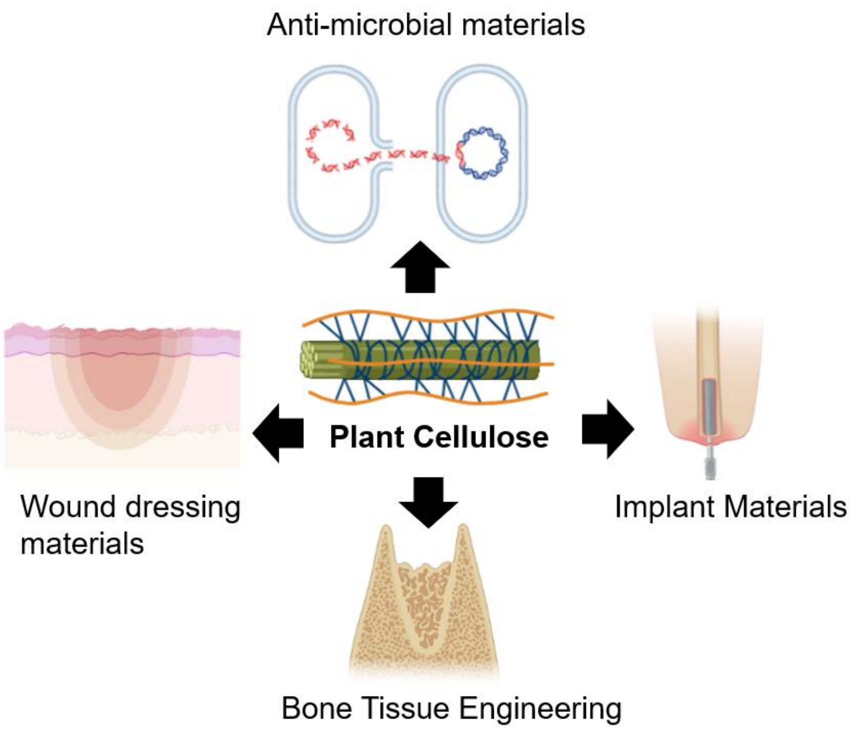

Figure 4. The potential of PC as a biomaterial in biomedical applications (created in BioRender.com)

4.1. Wound Healing Materials

A wound-healing process should maintain normal cellular function, moisture control, and optimal oxygen permeability [49]. PC is one of the biomaterials for wound healing with appropriate biological properties to accomplish this requirement [50]. Initially, The PC is always processed to obtain CNF and remove the PC impurities for biomaterial application. For wound dressing purposes, the CNFs are usually treated to get NCCs, transformed into aerogel for the process of drug absorption [51], processed with antimicrobial material [52], or enhanced with other polymer material to become a composite to improve the function of wound healing [53].

Bhatnagar et al. 2021 studied wound dressing material from chitosan (CS) hydrogel enhanced with kenaf NCCs hydrogel composite enhanced. The study was intended to stabilize the release of platelet lysate (PL) as therapeutic proteins for wound healing because the PL in treating wounds is drawback by its rapid degradation by proteases at the tissue site [54]. Therefore, the characteristics of the materials were measured through the parameter of physicochemical properties, *in vitro* cytocompatibility, cell proliferation, wound scratch assay, PL release, and CS stabilizing effect of the hydrogel composites. The result showed that the quantity of water retained in the short-term from the CS-NCCs-PL hydrogels increases, improving the PL release to wounded tissue and promoting cell proliferation.

Singla et al. 2015 developed nanocomposite (NCs) wound dressings by using NCCs isolated from *Syzygium cumini* leaves enhanced with silver nanoparticles (AgNPs) as an antimicrobial agent. The cytocompatibility was done through *in vivo* study of mice with acute and diabetic wounds. The result showed that the growth factor for cell proliferation increases, the extracellular matrix component, such as collagen, gains, and the pro-inflammatory factor decreases. This result indicates that the development of anti-microbial of NCs with optimized AgNPs concentration is effective wound management for accelerating the healing process.

Another potential of the PC as biomaterials for wound healing is proven by Modulevsky et al. 2016. They developed a scaffold made of decellularized cellulose derived from McIntosh red apples [55]. The biocompatibility examination was done *in vivo*, where the scaffold was implanted into the mice's bodies. The results showed collagen deposition as an extracellular matrix component in the dermis and blood vessel formation, indicating that this scaffold is biocompatible and has the potential as implanted material.

4.2. Bone Tissue Engineering Materials

In recent years, bone tissue engineering has arisen with revolutionary strategies for the *de novo* generation of new bone development employing biomaterials and cells that can mimic the physical and biological features of the extracellular matrix [56]. Biomaterials for bone tissue engineering must support bone growth, encourage the ingrowth of neighboring bone (osteoconductive), and integrate with the already-existing bone (osseointegration) [57]. Materials for bone tissue engineering have been created, engineered, and manufactured using various methods and biomaterials. One of the alternative biomaterials for bone tissue engineering is PC.

K. M. N’Gatta et al 2022 fabricated a scaffold with 3D printing composed of PLA (Polylactic acid) and NCC isolated from *Ficus thonningii* plant. The mineralization assay to check the osteoconductive characteristics of the PLA-NCC scaffold was done through the incubation of the scaffold in a simulated body fluid solution. The result shows that the scaffold can promote mineralization faster than PLA only. Moreover, the cytocompatibility tests revealed that the scaffold is compatible with and non-toxic for bone cells [58].

Fatemah et al 2022 developed a scaffold chitosan/NCC scaffold crosslinked with glutaraldehyde and calcium chloride. The treated scaffold has higher compressive strength and biomineralization ability. The in vitro analysis also showed that the cells can proliferate in the scaffold proving that this scaffold can be used as an alternative for bone tissue engineering [59].

Razek et al. 2016 conducted a study about the scaffold made of kenaf fiber. Kenaf fiber was coated by hydroxyapatite (HA) by immersing it in simulated body fluid containing hydroxyapatite molecules at different day intervals [60]. The result shows an increase in HA deposit while maintaining the mechanical characteristics of the kenaf fiber. This result indicates the possibility of the kenaf coated with HA as biomaterials for supporting bone growth.

4.3. Anti-microbial Materials

Antimicrobial materials include small molecules, macromolecules, polymers, ceramics, metals, or composites with microbicidal activities against microorganisms [61]. Most of the antimicrobial materials made of NCFs based aerogels incorporate antibacterial agents. Some of the antimicrobial agents that can be conjugated with NCFs are silver, zinc, lysozymes, and gentamicin [62]–[64].

V. T. Noronha et al. 2021 isolated the NCC from elephant grass (*Pennisetum purpureum*) leaves. NCCss dispersed in water and coated surfaces against *E. Coli* cells. The result shows that the NCCs are effective to inactivate the bacteria cells [65]. It confirmed the potential of NCCs to be applied for anti-microbial materials.

Y. Xiao et al fabricated a nano cellulose-based sponge followed by surface modification with gentamicin. The antibacterial activity was tested again *E.Coli and S. aureus*. The results show that Gentamicin-functionalized CNF sponges showed to prevent the activity of the bacteria with bactericidal rates of almost 100% [62].

4.4. Implant Materials

In general, Implant materials need to have three main characteristics; 1) Good bulk materials properties such as Young's modulus, ductility, and hardness; 2) Surface properties such as roughness and surface tension; 3) biocompatibility such as corrosion [66]. PC can full the requirement above as biomaterials for implants. PC is usually synthesized into different forms to reproduce as soft implant materials [67] or coating materials [68].

Daniel A. al. 2019 utilized NCC to fabricate sulfated NCC aerogel The study aimed to assess the potential of chemically cross-linked NCC aerogels as an alternative for an implant for bone. Two groups of rats are included in this study; the first group receives the aerogel implants and the second group is a control. Results showed that the group with implants has 33% more bone growth after the three-week mark and 50 % more bone growth at the 12-week mark, compared to the groups that did not receive the implant [69]. The study showed the potential of NCC for further development in implant materials research.

5. Conclusion

Plant-based cellulose (PC) is widely accepted as a biomaterial due to its biocompatibility with the biological environment in human tissues. Many studies have been carried out to fabricate and modify the PC for biomedical applications. This short review introduces how generally the PC is produced and utilized, the general characteristics of the PC as biomaterials, and the potential of the PC for biomedical applications. Recent advancements reveal that the PC has inherent properties that can be modified for various biomedical applications, including tissue engineering and the development of medication delivery and wound dressing systems. There is still a lot of room for the exploration of natural resources to maximize the potential of PC for biomedical applications. Furthermore, although PC does not show toxic characteristics, more research is required, such as further research in animal or human studies, assessing the potential pharmaceutical side effects, and biocompatibility profile. Moreover, modifying the physicochemical properties of the PC during production will inevitably incorporate the PC with foreign molecules that can cause biocompatibility issues. As a result, there are still multiple issues to be addressed and numerous avenues to pursue in this field.

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